

Hi David,

The PACT announcement seems to be taking shape for October 12 at 10 AM, at the National Press Club. Secy Price would preside. I have a meeting with him on Tuesday, and will need to brief him on PACT. I need to send read-ahead stuff by Friday. By tomorrow COB, can you send me a current 1 – 2 page summary useful for Secretarial inspection? And what's happened with our last lingering hold outs?

FC

Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$210 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, coordinating development of new biomarkers, filling knowledge gaps, and integrating information from multiple sources.

PACT will facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- Providing a set of basic biomarker modules for uniform clinical application.
- Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays. Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

PACT will also work to provide scientific coordination by facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

The core laboratory, assay development, and database functions required will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortuitously, NCI released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT. Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, the NCI plans to contribute ~\$160 million in funding over 5 years beginning in Fall 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize the use of existing biomarker assays so that they can be used efficiently in clinical trials of new medicines. These assays can be conducted in trials outside PACT yet channel data into the PACT database, provided the assays are performed to PACT standards.

(b) (4)

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.

Voting participation in the JSC and EC will be split 50/50 between government and private sector partners.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH's mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data, but consistent with these restrictions.

The value proposition for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- Access to core development laboratories and facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure quality evidence and documentation that enable potential registration and labeling
- Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

(b) (4) With confirmed partners, FNIH will reconvene the scientific leads to develop a final research plan, including detailed project plans and go/no-go milestones. Given the sense of urgency in addressing patient needs, the timing of NIH funding, and the rapid pace of progress in the field, formal launch of PACT is being targeted for Q1 of 2018.

From: Wholley, David (FNIH) [T]
Sent: Mon, 9 Oct 2017 17:05:47 +0000
To: Myles, Renate (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NCI)
Cc: Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Doroshow, James (NIH/NCI) [E]; Burklow, John (NIH/OD) [E]; Garrett, Peter (NIH/NCI) [E]; Lubenow, Anne (NIH/NCI) [E]; Adam, Stacey (FNIH) [T]; Hallett, Adrienne (NIH/OD) [E]; Berkson, Laura (NIH/OD) [E]; Wojtowicz, Emma (NIH/OD) [E]; Vitelli, Cynthia (NIH/NCI) [E]; Hatch, Shannon (NIH/NCI) [E]; Wood, Gretchen (NIH/OD) [E]; McManus, Ayanna (NIH/OD) [E]
Subject: RE: PACT Rollout Plan

I know she will not be acting as the patient representative, but should we not invite Ellen Sigal to attend? Stacey and I have briefed her several times on PACT (she is on the FNIH Board) and I think her support going forward with the cancer community and FDA will be very helpful.

(I am assuming Stacey, Maria, and I will attend from FNIH.)

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From: Myles, Renate (NIH/OD) [E]
Sent: Monday, October 09, 2017 12:48 PM
To: Lowy, Douglas (NIH/NCI) [E] (b) (6); Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NCI) (b) (6)
Cc: Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Garrett, Peter (NIH/NCI) [E] (b) (6); Lubenow, Anne (NIH/NCI) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Hallett, Adrienne (NIH/OD) [E] (b) (6); Berkson, Laura (NIH/OD) [E] (b) (6); Wojtowicz, Emma (NIH/OD) [E] (b) (6); Vitelli, Cynthia (NIH/NCI) [E] (b) (6); Hatch, Shannon (NIH/NCI) [E] (b) (6); Gretchen (NIH/OD) [E] (b) (6); McManus, Ayanna (NIH/OD) [E] (b) (6)
Subject: RE: PACT Rollout Plan

You mean we're lucky to get to have you! ☺

From: Lowy, Douglas (NIH/NCI) [E]
Sent: Monday, October 09, 2017 12:44 PM

To: Myles, Renate (NIH/OD) [E] (b) (6); Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NCI) (b) (6)
Cc: Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Garrett, Peter (NIH/NCI) [E] (b) (6); Lubenow, Anne (NIH/NCI) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Hallett, Adrienne (NIH/OD) [E] (b) (6); Berkson, Laura (NIH/OD) [E] (b) (6); Wojtowicz, Emma (NIH/OD) [E] (b) (6); Vitelli, Cynthia (NIH/NCI) [E] (b) (6); Hatch, Shannon (NIH/NCI) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6); McManus, Ayanna (NIH/OD) [E] (b) (6)
Subject: Re: PACT Rollout Plan

For the moment, you're stuck with me for NCI. I'll let you know if that changes. Doug

From: "Myles, Renate (NIH/OD) [E]" (b) (6)
Date: Monday, October 9, 2017 at 12:41 PM
To: "Lowy, Douglas" (b) (6); "Collins, Francis (NIH/OD) [E]" (b) (6); "Lowy, Douglas (NCI)" (b) (6)
Cc: "Tabak, Lawrence (NIH/OD) [E]" (b) (6); "Wolinetz, Carrie (NIH/OD) [E]" (b) (6); "Baker, Rebecca (NIH/OD) [E]" (b) (6); "Doroshow, James (NIH/NCI) [E]" (b) (6); "Burklow, John (NIH/OD) [E]" (b) (6); "Garrett, Peter (NIH/NCI) [E]" (b) (6); "Lubenow, Anne (NIH/NCI) [E]" (b) (6); "Wholley, David (FNIH) [T]" <dwholley@fnih.org>; "Adam, Stacey (FNIH) [T]" <sadam@fnih.org>; "Hallett, Adrienne (NIH/OD) [E]" (b) (6); "Berkson, Laura (NIH/OD) [E]" (b) (6); "Wojtowicz, Emma (NIH/OD) [E]" (b) (6); "Vitelli, Cynthia (NIH/NCI) [E]" (b) (6); "Hatch, Shannon (NIH/NCI) [E]" (b) (6); "Wood, Gretchen (NIH/OD) [E]" (b) (6); "McManus, Ayanna (NIH/OD) [E]" (b) (6)
Subject: RE: PACT Rollout Plan

Thanks for letting me know that Jim won't be there. Will there be other principals from NCI who will be attending who I should add to the list? And thanks for the catch of the typo on Maria's name.

From: Lowy, Douglas (NIH/NCI) [E]
Sent: Monday, October 09, 2017 12:39 PM
To: Myles, Renate (NIH/OD) [E] (b) (6); Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NCI) (b) (6)
Cc: Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Garrett, Peter (NIH/NCI) [E] (b) (6); Lubenow, Anne (NIH/NCI) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Hallett, Adrienne (NIH/OD) [E] (b) (6); Berkson, Laura

(NIH/OD) [E] (b) (6); Wojtowicz, Emma (NIH/OD) [E] (b) (6)
Vitelli, Cynthia (NIH/NCI) [E] (b) (6); Hatch, Shannon (NIH/NCI) [E]
(b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6); McManus, Ayanna
(NIH/OD) [E] (b) (6)

Subject: Re: PACT Rollout Plan

Thanks, Renate. 1) Placing me between the industry representative and Melinda is fine with me. 2) I would like to clarify that Jim Doroshow will not be there, as he had a long-standing commitment in the UK. 3) Dr. Freire's first name is Maria, rather than Marie. Doug

From: "Myles, Renate (NIH/OD) [E]" (b) (6)
Date: Monday, October 9, 2017 at 12:20 PM
To: "Collins, Francis (NIH/OD) [E]" (b) (6) "Lowy, Douglas (NCI)"
(b) (6)
Cc: "Tabak, Lawrence (NIH/OD) [E]" (b) (6), "Wolinetz, Carrie (NIH/OD) [E]"
(b) (6), "Baker, Rebecca (NIH/OD) [E]" (b) (6),
"Doroshow, James (NIH/NCI) [E]" (b) (6) "Burklow, John (NIH/OD) [E]"
(b) (6), "Garrett, Peter (NIH/NCI) [E]" (b) (6), "Lubenow,
Anne (NIH/NCI) [E]" (b) (6) "Wholley, David (FNIH) [T]"
<dwholley@fnihi.org>, "Adam, Stacey (FNIH) [T]" <sadam@fnihi.org>, "Hallett, Adrienne
(NIH/OD) [E]" (b) (6), "Berkson, Laura (NIH/OD) [E]"
(b) (6) "Wojtowicz, Emma (NIH/OD) [E]" (b) (6),
"Vitelli, Cynthia (NIH/NCI) [E]" (b) (6) "Hatch, Shannon (NIH/NCI) [E]"
(b) (6), "Wood, Gretchen (NIH/OD) [E]" (b) (6), "McManus,
Ayanna (NIH/OD) [E]" (b) (6)
Subject: RE: PACT Rollout Plan

Hi Francis and Doug:

Attached are the event details, including a proposed agenda. We thought it made sense if the Acting Secretary went first so he could leave after his remarks, if he so wishes. We also thought that the industry representative should go before Doug so that Doug can talk about the CIMACs and the CIDC and how these will support PACT efforts. We also thought it made more sense for Doug to introduce Melinda rather than have an industry person do that. Let me know if you agree.

The release is in HHS clearance and has also been shared with all of the partner organizations for a partner quotes and bios. We are still waiting to hear from partner organizations on their participation in the event. Currently, only GSK, Pfizer and Janssen have confirmed participation. We expect to hear from Dr. Tom Hudson of AbbVie today on whether he is able to speak on behalf of industry partners. BMS and Celgene declined and did not offer a substitute. We will keep you posted as this develops.

Best,
Renate

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, October 05, 2017 8:25 PM

To: Myles, Renate (NIH/OD) [E] (b) (6)
Cc: Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Lowy, Douglas (NCI) (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Garrett, Peter (NIH/NCI) [E] (b) (6); Lubenow, Anne (NIH/NCI) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Adam, Stacey (FNIH) [T] <sadam@fnihi.org>; Hallett, Adrienne (NIH/OD) [E] (b) (6); Berkson, Laura (NIH/OD) [E] (b) (6); Wojtowicz, Emma (NIH/OD) [E] (b) (6); Vitelli, Cynthia (NIH/NCI) [E] (b) (6); Hatch, Shannon (NIH/NCI) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6); McManus, Ayanna (NIH/OD) [E] (b) (6)
Subject: RE: PACT Rollout Plan

Looks good. But we need to clarify the run of show for the actual event. Acting Secy Don Wright sounded willing when I spoke to him last Tuesday, but I don't think that's been put on his calendar yet. And rumor has it that we might have a new Acting Secy (Eric Hargan) by next week.

We had discussed having Sandra Horning (Roche/Genentech) as the industry speaker. Have we heard from her about whether she's planning to come?

FC

From: Myles, Renate (NIH/OD) [E]
Sent: Thursday, October 05, 2017 10:36 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Lowy, Douglas (NCI) (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Garrett, Peter (NIH/NCI) [E] (b) (6); Lubenow, Anne (NIH/NCI) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Adam, Stacey (FNIH) [T] <sadam@fnihi.org>; Hallett, Adrienne (NIH/OD) [E] (b) (6); Berkson, Laura (NIH/OD) [E] (b) (6); Wojtowicz, Emma (NIH/OD) [E] (b) (6); Vitelli, Cynthia (NIH/NCI) [E] (b) (6); Hatch, Shannon (NIH/NCI) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6); McManus, Ayanna (NIH/OD) [E] (b) (6)
Subject: PACT Rollout Plan

Good morning, Francis:

Attached is the PACT rollout plan. The release and media availability were sent to FNIH this morning for review and we hope to have them to you this afternoon for final review, after NCI coordinates review by Doug and Jim. I will be out of the office today and tomorrow, so Emma will keep things moving.

Best,
Renate

From: Wholley, David (FNIH) [T]
Sent: Thu, 5 Oct 2017 14:51:31 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]
Subject: RE: PACT

Yeahh!

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From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, October 05, 2017 10:45 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: Fwd: PACT

Woo hoo!

Sent from my iPhone

Begin forwarded message:

From: "Bradner, James" <james.bradner@novartis.com>
Date: October 5, 2017 at 9:58:48 AM EDT
To: "Collins, Francis (NIH/OD) [E]" (b) (6)
Cc: "Rammohan, Revathi" <revathi.rammohan@novartis.com>, "Brown, Scott" <scott.brown@novartis.com>, "Engelman, Jeffrey" <jeffrey.engelman@novartis.com>, "Hammerman, Peter" <peter.hammerman@novartis.com>, "Dranoff, Glenn" <glenn.dranoff@novartis.com>, "Petruzzelli, Lilli" <lilli.petruzzelli@novartis.com>, "Lockwood, Jeffrey" <jeffrey.lockwood@novartis.com>
Subject: PACT

francis.

thank you for the invitation to steer and now join the NIH-PACT program focused on cancer immunotherapy biomarker discovery. this week we assembled our cancer and institutional leadership (many cc'd here), to examine the clarified design principles emerging from the workstream and to assess alignment with our critical path in IO and cancer medicine. we applaud the effort to pull together so many leading institutions and scientists around this generational activity. we agree violently that the

development of next-generation IO agents will require new measurements guiding use and explaining (in)activity. in this regard, we are well aligned with the program and would like to participate.

my sense is that there are important strategic details still to define, regarding scientific focus, institutions/scientific leaders involved, clarified and prioritized measurements. jeff, peter, glenn and lilli cc'd will surely have helpful guidance, should the PACT welcome insights at this pivotal stage. candidly, our principal interest remains connected to the safe harbor the PACT might provide for combination clinical trials of next-gen agents between companies. we would welcome a chance to work with peer institutions through the NIH network. but even with a focus on biomarker creation, curation and deployment, we are motivated to join. i defer to jeff to provide guidance as to how best and who best to contribute these and other guidance.

(b) (4)

finally, we are working hard to help you hit your deadline on the announcement and would like to be a party to the announcement. peter can join in DC at the national press club, if this invitation is still open and helpful.

thank you for the invitation, again, to join. we so admire the heroic work you continue to lead, orienting our government around this rarified moment in biomedicine, openly assembling diverse research communities, and always defending basic research.

please advise on next steps.

best - jay

--

Jay Bradner, M.D.

President | Novartis Institutes for BioMedical Research

[james.bradner\[at\]novartis.com](mailto:james.bradner@novartis.com)

From: Wholley, David (FNIH) [T]
Sent: Wed, 6 Sep 2017 17:47:38 +0000
To: Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Mott, Meghan (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]
Subject: RE: Pain PPP slides -- still need some fix ups
Attachments: September meeting tracker.xlsx

Francis, all –

Just thinking about tomorrow's call - as you know I always am at least a little concerned about audience participation on some of these kinds of telecons—there are times when we ask for feedback from industry on a proposal and for one reason or another hear crickets. To avoid this, I would suggest we be prepared to proactively call on specific folks by name with one or more questions to get the ball rolling, in the event no one takes up the question. Looking over the latest version of the roster for tomorrow that I have from Rebecca (attached) and assuming all these folks show up I would go with the reps from Pfizer and Lilly, as their companies clearly are large and engaged enough in the pain space to have something to say:

Mark Mintun joined Lilly from Avid Radiopharmaceuticals, has been very positively involved in AMP AD, and will no doubt bring an imaging slant to the discussion.

Ken Verburg (SVP, Global Head of Development at Pfizer) would be the most senior of the group if he shows up. If not, Michael Maher is a decent second—works as staff to Mikael Dolsten on external alliance activities.

Does anyone else have suggestions?

Thanks, David
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From: Wolinetz, Carrie (NIH/OD) [E]
Sent: Wednesday, September 06, 2017 11:25 AM
To: Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T]
<dwholley@fnih.org>; Collins, Francis (NIH/OD) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E]
(b) (6) Porter, Linda (NIH/NINDS) [E] (b) (6) Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6) Stein, Jack (NIH/NIDA) [E] (b) (6)
Subject: RE: Pain PPP slides -- still need some fix ups

Rebecca,

I just tweaked to make the bullets a consistent format. Cheers, Carrie

From: Baker, Rebecca (NIH/OD) [E]

Sent: Wednesday, September 06, 2017 10:32 AM

To: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Collins, Francis (NIH/OD) [E] (b) (6);

Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E]

(b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie

(NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6);

Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6)

Subject: RE: Pain PPP slides -- still need some fix ups

Thanks David,

Attached please find a revised draft set of slides incorporating David's great suggestions.

Are others still waiting to weigh in with additional edits?

Thanks,

Rebecca

From: Wholley, David (FNIH) [T]

Sent: Wednesday, September 06, 2017 10:06 AM

To: Collins, Francis (NIH/OD) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E]

(b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan

(NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6)

Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E]

(b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack

(NIH/NIDA) [E] (b) (6)

Subject: RE: Pain PPP slides -- still need some fix ups

(b) (5)

Thanks, David

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From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, September 06, 2017 6:14 AM
To: Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: RE: Pain PPP slides -- still need some fix ups

Getting much better. I did a bit more tweaking, (b) (5), since that's what your slide suggested it would be. Hopefully this is now about ready to go.

FC

From: Koroshetz, Walter (NIH/NINDS) [E]
Sent: Tuesday, September 05, 2017 10:59 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Wholley, David (FNIH) [T]

<dwholley@fnihi.org>

Subject: RE: Pain PPP slides -- still need some fix ups

Thanks Francis. Looks clean. I rearranged the order of the enumerated programs to fit your slide 32.

(b) (5)

Thanks for everyone's help on this.

Walter

From: Collins, Francis (NIH/OD) [E]

Sent: Tuesday, September 05, 2017 9:36 PM

To: Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>

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(b) (5)

We're really getting down to the wire, and need to send this out by tomorrow afternoon. Can I see a new version by mid-morning tomorrow?

Thanks, everyone.

Francis

From: Wholley, David (FNIH) [T]
Sent: Wed, 6 Sep 2017 14:06:10 +0000
To: Collins, Francis (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Baker, Rebecca (NIH/OD) [E]; Mott, Meghan (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]
Subject: RE: Pain PPP slides -- still need some fix ups

(b) (5)



Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, September 06, 2017 6:14 AM
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Subject: RE: Pain PPP slides -- still need some fix ups

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(b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Wholley, David (FNIH) [T]
<dwholley@fnih.org>

Subject: Pain PPP slides -- still need some fix ups

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We're really getting down to the wire, and need to send this out by tomorrow afternoon. Can I see a new version by mid-morning tomorrow?

Thanks, everyone.

Francis

From: Wholley, David (FNIH) [T]
Sent: Thu, 7 Sep 2017 01:55:29 +0000
To: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Cc: Wolinetz, Carrie (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Mott, Meghan (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]
Subject: Re: Pain PPP slides -- still need some fix ups

Really great if Elias joins the group tomorrow. If not, Rita Balice-Gordon has been lead on AMP PD and is a good egg. (b) (4), (b) (5)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, September 6, 2017 7:15 PM
To: Baker, Rebecca (NIH/OD) [E]
Cc: Wholley, David (FNIH) [T]; Wolinetz, Carrie (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Mott, Meghan (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]
Subject: RE: Pain PPP slides -- still need some fix ups

Please remind us which of these folks attended one of the NIH workshops.

Certainly Elias will be a good person to call on if there's silence.

FC

From: Baker, Rebecca (NIH/OD) [E]
Sent: Wednesday, September 06, 2017 7:12 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Wolinetz, Carrie (NIH/OD) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6)
Subject: Re: Pain PPP slides -- still need some fix ups

Hi FC, out of pocket but pasting below the latest roster I just received from PhRMA. Will bring updates agendas tomorrow AM. Bill Chin plans to run through the roster at the top of the call.

Steve Ryder (Alexion)

Eliot Ehrich (Alkermes)

John Dunlop (Amgen)
Kate Dawson (Biogen)
Maria Palmisano (Cellegene)
Ken Truitt (Daiichi Sankyo)
Yuko Kimura (Daiichi Sankyo)
Lynn Kramer (Eisai)
Min Li (GSK)
Chris Flores (Janssen)
Aran Maree (Janssen)
David Michelson (Merck)
Ricardo Dolmetsch (Novartis)
Tim Peters-Strickland (Otsuka)
Don Kyle (Purdue)
Rita Balice-Gordon (Sanofi)
Elias Zerhouni (Sanofi)
Ken Koblan (Sunovion)
Emilio Merlo Pich (Takeda)
Ernest Kopecky (Teva)
Janet Vessotskie (UCB)

Sent from my iPhone

On Sep 6, 2017, at 6:40 PM, Collins, Francis (NIH/OD) [E] (b) (6) wrote:

Hi all,

Like David, I'm worried about there being long silences from industry colleagues on tomorrow's call – especially because we start off with a trio of NIH presentations that might make it seem that this PPP is already fully baked. I will need to emphasize that is NOT the case in my opening remarks.

I'm not sure whether Mark Mintun is actually going to participate – Rebecca, is that correct? Is this the most up to date roster? And are there any other participants in the telecon who attended one of the NIH workshops?

Certainly Ken Verburg would be a natural, since he attended one of the workshops and was a very helpful voice.

Nora, is there someone you would want to call on for Project #1?

Francis

From: Wholley, David (FNIH) [T]

Sent: Wednesday, September 06, 2017 1:48 PM

To: Wolinetz, Carrie (NIH/OD) [E] (b) (6) Baker, Rebecca (NIH/OD) [E]
(b) (6); Collins, Francis (NIH/OD) [E] (b) (6) Koroshetz, Walter
(NIH/NINDS) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E]
(b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Tabak, Lawrence
(NIH/OD) [E] (b) (6) Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein,
Jack (NIH/NIDA) [E] (b) (6)

Subject: RE: Pain PPP slides -- still need some fix ups

Francis, all –

Just thinking about tomorrow's call - as you know I always am at least a little concerned about audience participation on some of these kinds of telecons—there are times when we ask for feedback from industry on a proposal and for one reason or another hear crickets. To avoid this, I would suggest we be prepared to proactively call on specific folks by name with one or more questions to get the ball rolling, in the event no one takes up the question. Looking over the latest version of the roster for tomorrow that I have from Rebecca (attached) and assuming all these folks show up I would go with the reps from Pfizer and Lilly, as their companies clearly are large and engaged enough in the pain space to have something to say:

Mark Mintun joined Lilly from Avid Radiopharmaceuticals, has been very positively involved in AMP AD, and will no doubt bring an imaging slant to the discussion.

Ken Verburg (SVP, Global Head of Development at Pfizer) would be the most senior of the group if he shows up. If not, Michael Maher is a decent second—works as staff to Mikael Dolsten on external alliance activities.

Does anyone else have suggestions?

Thanks, David

David Wholley

Director, Research Partnerships

Foundation for the National Institutes of Health

(301) 594-6343

fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wolinetz, Carrie (NIH/OD) [E]
Sent: Wednesday, September 06, 2017 11:25 AM
To: Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T]
<dwholley@fnihi.org>; Collins, Francis (NIH/OD) [E] (b) (6); Koroshetz, Walter
(NIH/NINDS) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E]
(b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Tabak, Lawrence
(NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein,
Jack (NIH/NIDA) [E] (b) (6)
Subject: RE: Pain PPP slides -- still need some fix ups

Rebecca,

I just tweaked to make the bullets a consistent format. Cheers, Carrie

From: Baker, Rebecca (NIH/OD) [E]
Sent: Wednesday, September 06, 2017 10:32 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Collins, Francis (NIH/OD) [E] (b) (6);
Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E]
(b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie
(NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6);
Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6)
Subject: RE: Pain PPP slides -- still need some fix ups

Thanks David,

Attached please find a revised draft set of slides incorporating David's great suggestions.
Are others still waiting to weigh in with additional edits?

Thanks,
Rebecca

From: Wholley, David (FNIH) [T]
Sent: Wednesday, September 06, 2017 10:06 AM
To: Collins, Francis (NIH/OD) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E]
(b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan
(NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6);
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Subject: RE: Pain PPP slides -- still need some fix ups

(b) (5)

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To: Collins, Francis (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>
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To: Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Mott, Meghan (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>
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Thanks, everyone.

Francis

From: Wholley, David (FNIH) [T]
Sent: Mon, 9 Oct 2017 03:00:36 +0000
To: (b) (4); Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; (b) (4)
Subject: Re: Partnership to Accelerate Cancer Therapies (PACT)

H (b) (4), is there a good time for me to call you tomorrow?
Sent from my BlackBerry 10 smartphone.

From: (b) (4)
Sent: Sunday, October 8, 2017 6:10 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Wholley, David (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; (b) (4)
Subject: Re: Partnership to Accelerate Cancer Therapies (PACT)

Dear Francis,

(b) (4)

On Oct 2, 2017, at 2:38 PM, Collins, Francis (NIH/OD) [E] (b) (6) wrote:

Dear (b) (4),

I wanted to give you an update on the Partnership to Accelerate Cancer Therapies (PACT). As you may recall NIH worked with FNIH, FDA, and 14 pharmaceutical companies (b) (4) earlier this year to plan a public-private partnership that would help coordinate the development of standardized biomarkers and assays needed to conduct trials of new cancer immunotherapies and combination therapies. The resulting plan builds on a \$160 million investment by NCI over 5 years in core laboratory and database infrastructure with (b) (4) to expand the number of novel markers, assays, and types of data that can be developed.

(b) (4)

(b) (4) As a result, we now have eight companies pledged to support PACT, and will be holding an announcement at the National Press Club here in Washington on October 12 with all of the participants.

(b) (4)

Warm regards, Francis

<Updated PACT Executive Summary 092617.docx>

From: Wholley, David (FNIH) [T]
Sent: Wed, 13 Dec 2017 00:59:37 +0000
To: Biarnes, Michael (FNIH) [T]; Collins, Francis (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E]; Austin, Christopher (NIH/NCATS) [E]; Colvis, Christine (NIH/NCATS) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Menetski, Joseph (FNIH) [T]
Subject: Re: Partnership to Address the Opioids Crisis - Day 1 Summary

PS, we know the slides representing Nora's and Chris F.'s summations may repeat some earlier points but wanted to remind you what they felt were the key priorities. Hopefully we did not miss anything major.

Sent from my BlackBerry 10 smartphone.

From: Biarnes, Michael (FNIH) [T]
Sent: Tuesday, December 12, 2017 7:42 PM
To: Collins, Francis (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E]; Austin, Christopher (NIH/NCATS) [E]; Colvis, Christine (NIH/NCATS) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wholley, David (FNIH) [T]; Menetski, Joseph (FNIH) [T]
Subject: Partnership to Address the Opioids Crisis - Day 1 Summary

Dear all,

Please find the key decisions and action items that we noted from today's call attached for your review. The plan is for these to be reviewed by Drs. Collins and Flores with the group during the Meeting Summary to end tomorrow. Please let us know if any edits are needed.

Thanks,
Mike

We've moved! Please find our new address below.

Michael Biarnes

Scientific Project Manager

Foundation for the National Institutes of Health

(301) 594-2612

fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

The FNIH is the #1 ranked biomedical research charitable organization & earned a 4-star rating from [Charity Navigator](#).

From: Wholley, David (FNIH) [T]
Sent: Wed, 13 Dec 2017 12:18:28 +0000
To: Stein, Jack (NIH/NIDA) [E]; Baker, Rebecca (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Volkow, Nora (NIH/NIDA) [E]; Biarnes, Michael (FNIH) [T]; cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E]; Austin, Christopher (NIH/NCATS) [E]; Colvis, Christine (NIH/NCATS) [E]
Cc: Menetski, Joseph (FNIH) [T]
Subject: Re: Partnership to Address the Opioids Crisis - Day 1 Summary

(b) (4)

Sent from my BlackBerry 10 smartphone.

From: Stein, Jack (NIH/NIDA) [E]
Sent: Wednesday, December 13, 2017 7:08 AM
To: Baker, Rebecca (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Volkow, Nora (NIH/NIDA) [E]; Biarnes, Michael (FNIH) [T]; cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E]; Austin, Christopher (NIH/NCATS) [E]; Colvis, Christine (NIH/NCATS) [E]
Cc: Wholley, David (FNIH) [T]; Menetski, Joseph (FNIH) [T]
Subject: RE: Partnership to Address the Opioids Crisis - Day 1 Summary

Summary indeed looking good!
3 thinks to consider :

(b) (4)

Jack
Sent with BlackBerry Work
(www.blackberry.com)

From: Baker, Rebecca (NIH/OD) [E] (b) (6)
Date: Wednesday, Dec 13, 2017, 6:35 AM
To: Collins, Francis (NIH/OD) [E] (b) (6), Koroshetz, Walter (NIH/NINDS) [E] (b) (6), Volkow, Nora (NIH/NIDA) [E] (b) (6), Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>, Stein, Jack (NIH/NIDA) [E] (b) (6), cflores2@its.jnj.com <cflores2@its.jnj.com>, osman.cigeroglu@pfizer.com <osman.cigeroglu@pfizer.com>, jdunlop@amgen.com <jdunlop@amgen.com>, Oshinsky, Michael (NIH/NINDS) [E] (b) (6), Austin, Christopher (NIH/NCATS) [E] (b) (6), Colvis, Christine (NIH/NCATS) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>, Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>
Subject: RE: Partnership to Address the Opioids Crisis - Day 1 Summary

Francis,

Please find a slightly revised version attached.

Thanks,
Rebecca

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, December 12, 2017 8:47 PM
To: Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Biarnes, Michael (FNIH) [T] <mbiarnes@fnihi.org>; Stein, Jack (NIH/NIDA) [E] (b) (6); cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E] (b) (6); Austin, Christopher (NIH/NCATS) [E] (b) (6); Colvis, Christine (NIH/NCATS) [E] (b) (6)
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Subject: RE: Partnership to Address the Opioids Crisis - Day 1 Summary

Appreciate Michael's excellent draft, and the edits/comments from Walter and Nora. Others may also want to comment.

I'll hold off making any further suggestions until tomorrow AM.

FC

From: Koroshetz, Walter (NIH/NINDS) [E]
Sent: Tuesday, December 12, 2017 8:43 PM
To: Volkow, Nora (NIH/NIDA) [E] (b) (6); Biarnes, Michael (FNIH) [T] <mbiarnes@fnihi.org>; Collins, Francis (NIH/OD) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E] (b) (6); Austin, Christopher (NIH/NCATS) [E] (b) (6); Colvis, Christine (NIH/NCATS) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnihi.org>
Subject: RE: Partnership to Address the Opioids Crisis - Day 1 Summary

Few edits on pain slides in red.
walter

From: Volkow, Nora (NIH/NIDA) [E]
Sent: Tuesday, December 12, 2017 8:40 PM
To: Biarnes, Michael (FNIH) [T] <mbiarnes@fnihi.org>; Collins, Francis (NIH/OD) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); cflores2@its.jnj.com; osman.cigeroglu@pfizer.com; jdunlop@amgen.com; Oshinsky, Michael (NIH/NINDS) [E] (b) (6); Austin, Christopher (NIH/NCATS) [E] (b) (6); Colvis, Christine (NIH/NCATS) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T]

<dwholley@fnihi.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnihi.org>

Subject: Re: Partnership to Address the Opioids Crisis - Day 1 Summary

Michael I did some editing the OUD slides nora

From: "Biarnes, Michael (FNIH) [T]" <mbiarnes@fnihi.org>

Date: Tuesday, December 12, 2017 at 7:42 PM

To: Francis Collins (b) (6), Walter Koroshetz (b) (6), Nora Volkow (b) (6), Jack Stein (b) (6), "cflores2@its.jnj.com"

<cflores2@its.jnj.com>, "osman.cigeroglu@pfizer.com" <osman.cigeroglu@pfizer.com>, "jdunlop@amgen.com" <jdunlop@amgen.com>, "Oshinsky, Michael (NIH/NINDS) [E]"

(b) (6), "Austin, Christopher (NIH/NCATS) [E]" (b) (6), "Colvis, Christine (NIH/NCATS) [E]" (b) (6)

Cc: "Baker, Rebecca (NIH/OD) [E]" (b) (6), "Wholley, David (FNIH) [T]" <dwholley@fnihi.org>, "Menetski, Joseph (FNIH) [T]" <jmenetski@fnihi.org>

Subject: Partnership to Address the Opioids Crisis - Day 1 Summary

Dear all,

Please find the key decisions and action items that we noted from today's call attached for your review. The plan is for these to be reviewed by Drs. Collins and Flores with the group during the Meeting Summary to end tomorrow. Please let us know if any edits are needed.

Thanks,
Mike

We've moved! Please find our new address below.

Michael Biarnes

Scientific Project Manager

Foundation for the National Institutes of Health

(301) 594-2612

fnihi.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

The FNIH is the #1 ranked biomedical research charitable organization & earned a 4-star rating from Charity Navigator.

From: Wholley, David (FNIH) [T]
Sent: Wed, 6 Dec 2017 01:12:42 +0000
To: Collins, Francis (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]
Cc: Baker, Rebecca (NIH/OD) [E]; Menetski, Joseph (FNIH) [T]
Subject: RE: Partnership to Address the Opioids Crisis Focus Area B Co-Chair Call

Francis, Mike just reminded me that this conflicts with your regularly scheduled update meeting (sorry but lots and lots of calls lately as you know). We apologize for the scheduling conflict, but this was absolutely the only time we could make this call work for a majority of the co-chairs even with weeks of notice, and I know it too is a call you specifically suggested.

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, December 5, 2017 7:36 PM
To: Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>
Subject: Re: Partnership to Address the Opioids Crisis Focus Area B Co-Chair Call

Thanks for the heads up!

Sent from my iPhone

On Dec 5, 2017, at 4:56 PM, Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org> wrote:

Dear Francis,

On Thursday we will be holding a meeting with the Focus Area B working group co-chairs from 12-2pm ET to discuss the progress of the working groups to date, structure of the face-to-face meeting, outline of the working group slides, and materials needed ahead of the face-to-face meeting. While we will necessarily be focused on preparing the pain effort for next week's face to face meeting, we have also invited Nora and Jack to join the call as it may be helpful to insure cohesion between the two Focus Areas. We just wanted you to know about the call in case it was not on your calendar and you wanted to join in for any reason.

Best,
Mike

We've moved! Please find our new address below.

Michael Biarnes

Scientific Project Manager

Foundation for the National Institutes of Health

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11400 Rockville Pike Suite 600 North Bethesda, MD 20852

The FNIH is the #1 ranked biomedical research charitable organization & earned a 4-star rating from Charity Navigator.

From: Wholley, David (FNIH) [T]
Sent: Wed, 11 Oct 2017 16:15:22 +0000
To: Myles, Renate (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Adam, Stacey (FNIH) [T]; Meltzer, Abbey (FNIH) [T]
Subject: RE: PLEASE REVIEW FINAL RELEASE
Attachments: DRAFT_Release_PACT_10.6.17_ASPA Clearance V2dw.docx

Here are my changes (in blue). Our comms person has also looked at this.

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, October 11, 2017 11:33 AM
To: Collins, Francis (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E]
(b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: PLEASE REVIEW FINAL RELEASE
Importance: High

Hi Francis and David:

Attached is the final release that is marked up with company input. I'm still waiting for Hargan's quote, but would you confirm that the numbers are accurate? We plan to reproduce these for the press packs this afternoon.

Thanks,
Renate

From: Wholley, David (FNIH) [T]
Sent: Wed, 11 Oct 2017 18:08:52 +0000
To: Collins, Francis (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Adam, Stacey (FNIH) [T]; Meltzer, Abbey (FNIH) [T]
Subject: RE: PLEASE REVIEW FINAL RELEASE

(b) (4), (b) (5)

(b) (4), (b) (5) David

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Director, Research Partnerships
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From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, October 11, 2017 1:33 PM
To: Myles, Renate (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Burklow, John (NIH/OD) [E] (b) (6) Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Meltzer, Abbey (FNIH) [T] <ameltzer@fnih.org>
Subject: RE: PLEASE REVIEW FINAL RELEASE

(b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Wednesday, October 11, 2017 12:15 PM
To: Myles, Renate (NIH/OD) [E] (b) (6); Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Meltzer, Abbey (FNIH) [T] <ameltzer@fnih.org>
Subject: RE: PLEASE REVIEW FINAL RELEASE

Here are my changes (in blue). Our comms person has also looked at this.

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From: Myles, Renate (NIH/OD) [E]
Sent: Wednesday, October 11, 2017 11:33 AM
To: Collins, Francis (NIH/OD) [E] (b) (6) Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6) Burklow, John (NIH/OD) [E]
(b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: PLEASE REVIEW FINAL RELEASE
Importance: High

Hi Francis and David:

Attached is the final release that is marked up with company input. I'm still waiting for Hargan's quote, but would you confirm that the numbers are accurate? We plan to reproduce these for the press packs this afternoon.

Thanks,
Renate

From: Wholley, David (FNIH) [T]
Sent: Wed, 6 Dec 2017 17:28:44 +0000
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Subject: RE: Proposed agenda for Opioids Partnership F2F next week

Mike is revising the agenda accordingly. We'll insert Bill (or Rich) right after you, within a common block of time.

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, December 6, 2017 12:13 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Tabak, Lawrence (NIH/OD) [E]
(b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6)
Subject: RE: Proposed agenda for Opioids Partnership F2F next week

To the extent possible, it would be good to maintain a similar structure for the meeting sessions on Focus A and B.

And I'm fine with a brief welcome from PhRMA.

FC

From: Wholley, David (FNIH) [T]
Sent: Tuesday, December 05, 2017 8:19 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6)
Subject: FW: Proposed agenda for Opioids Partnership F2F next week

Thoughts? Happy to make changes. By the way, I don't think our budgeting segment is going to address actual estimates at this point—too early in most cases—but will rather discuss strategies for coming to such general estimations in the white paper writing process.

From: Chin, Bill [<mailto:Chin@phrma.org>]
Sent: Tuesday, December 5, 2017 5:47 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>; Menetski, Joseph (FNIH) [T] <jmenetski@fnih.org>; Moscicki, Richard <rmoscicki@phrma.org>
Subject: RE: Proposed agenda for Opioids Partnership F2F next week

David, Two thoughts. First, on 12/13 you have scheduled a session entitled, "Focus Area B: Refinement and Budgeting." But there is not analogous session for Focus Area A. Second, I think you should let PhRMA join Francis in the Introduction to ensure the optics reflect the PPP. You don't even need to list either me or Rich but one of us should welcome everyone and particularly get a chance to thank the industry members for their participation. My two cents. Bill

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnih.org>]

Sent: Tuesday, December 05, 2017 1:31 PM

To: Chin, Bill

Cc: Baker, Rebecca (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]

Subject: Proposed agenda for Opioids Partnership F2F next week

Bill, please see the attached, result of our conversations with the NIH group so far, but pending input from the co-chairs and finalization. Please let me know if anything looks amiss.

David

We've moved! Please find our new address below.

David Wholley

Director, Research Partnerships

Foundation for the National Institutes of Health

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fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

*Learn more about the FNIH in our **2016 Annual Report**: fnih.org/AnnualReport.*

From: Wholley, David (FNIH) [T]
Sent: Sun, 10 Sep 2017 18:48:34 +0000
To: (b) (4); Collins, Francis (NIH/OD) [E]
Cc: (b) (4)
Subject: Re: PACT (b) (4)

Hi (b) (4),

(b) (4)

(b) (4) Please let us know if there are any questions remaining to be answered and we will be happy to jump on the phone.

Regards,
David Wholley
Foundation for the NIH
Sent from my BlackBerry 10 smartphone.

From: (b) (4)
Sent: Sunday, September 10, 2017 9:55 AM
To: Collins, Francis (NIH/OD) [E]
Cc: Wholley, David (FNIH) [T]; (b) (4)
Subject: Re: PACT (b) (4)

Thank you, Francis.

(b) (4)

(b) (4)

From: "Collins, Francis (NIH/OD) [E]" (b) (6)
Date: Saturday, September 9, 2017 at 5:08 PM

To: [REDACTED] (b) (4)
Cc: "Wholley, David (FNIH) [T]" <dwholley@fnihi.org>
Subject: PACT [REDACTED] (b) (4)

(b) (4)

Many thanks, Francis

From: Wholley, David (FNIH) [T]
Sent: Sun, 10 Sep 2017 18:50:56 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: Re: PACT (b) (4)

(b) (4)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Sunday, September 10, 2017 2:49 PM
To: Wholley, David (FNIH) [T]
Subject: RE: PACT (b) (4)

You beat me to it, thanks.

From: Wholley, David (FNIH) [T]
Sent: Sunday, September 10, 2017 2:49 PM
To: (b) (4) Collins, Francis (NIH/OD) [E] (b) (6)
Cc: (b) (4);
(b) (4)
Subject: Re: PACT (b) (4)

(b) (4)

(b) (4) Please let us know if there are any questions remaining to be answered and we will be happy to jump on the phone.

Regards,
David Wholley
Foundation for the NIH
Sent from my BlackBerry 10 smartphone.

From: (b) (4)
Sent: Sunday, September 10, 2017 9:55 AM
To: Collins, Francis (NIH/OD) [E]
Cc: Wholley, David (FNIH) [T]; (b) (4)
Subject: Re: PACT (b) (4)

Thank you, Francis.

(b) (4)

(b) (4)

From: "Collins, Francis (NIH/OD) [E]" (b) (6)

Date: Saturday, September 9, 2017 at 5:08 PM

To: (b) (4)

Cc: "Wholley, David (FNIH) [T]" <dwholley@fnihi.org>

Subject: PACT (b) (4)

(b) (4)

Many thanks, Francis

From: Wholley, David (FNIH) [T]
Sent: Thu, 21 Sep 2017 21:59:25 +0000
To: Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Schwetz, Tara (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Hallett, Adrienne (NIH/OD) [E]
Cc: McManus, Ayanna (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]
Subject: RE: PACT announcement timing

(b) (4)

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, September 21, 2017 3:59 PM
To: Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Schwetz, Tara (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Myles, Renate (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Hallett, Adrienne (NIH/OD) [E] (b) (6)
Cc: McManus, Ayanna (NIH/OD) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6)
Subject: PACT announcement timing

Hi all,

After a brief flirtation with a National Press Club announcement of PACT on Sept. 28, presided over by Secretary Price (and possibly also Ivanka Trump), it appears this won't work. Secretary Price is not available.

But that was awfully short notice for us to pull everything together anyway. And the participating companies would no doubt like to have more notice than just one week.

Doug Lowy tells me that NCI could make their relevant FY17 awards now, but keep any announcement about those quiet until the time of a PACT roll out.

So let's plan on doing this in early October instead. It might be best to avoid October 5 because of the opioid hearing, don't want to confuse all of the partnership discussions. October 10 and 12 look good to me right now. [REDACTED] (b) (4)

[REDACTED] John, can you explore some possible mornings where this would work, and work with ASPA to get on the Secretary's schedule?

I'll send a note to Reed Cordish right now.

FC

From: Wholley, David (FNIH) [T]
Sent: Mon, 25 Sep 2017 01:47:14 +0000
To: Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Hallett, Adrienne (NIH/OD) [E]
Subject: Re: PACT announcement

Yes., thanks.

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Saturday, September 23, 2017 4:59 PM
To: Wholley, David (FNIH) [T]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Hallett, Adrienne (NIH/OD) [E]
Subject: PACT announcement

Hi all,

As you can see from the thread below, we are closing in on 10 AM October 12 for a PACT launch announcement at the Press Club. Secretary Price will speak. Not certain about the White House representation, might be brief remarks from Reed Cordish. We need to figure out who else should speak and what the order would be.

Doug, Jim, and David, does that sound like a feasible date and time?

Francis

From: Myles, Renate (NIH/OD) [E]
Sent: Saturday, September 23, 2017 8:14 AM
To: Collins, Francis (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E]
(b) (6)
Subject: Re: Pressing need to discuss four items with you

Yes, I reserved the room for that date and time. I would need to put a contract down to secure it though. Will you send a note the larger group to find out NCI's availability and that of the participating organizations?

From: Collins, Francis (NIH/OD) [E]
Sent: Friday, September 22, 2017 10:44 PM
To: Burklow, John (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]
Subject: FW: Pressing need to discuss four items with you

Much better, can we get the Press Club?

From: Lapinski, Mary-Sumpter (HHS/IOS) (b) (6)
Sent: Friday, September 22, 2017 3:19 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Myles, Renate (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6)
Subject: RE: Pressing need to discuss four items with you

After sharing your feedback with them, they now are holding 10-11am.

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Friday, September 22, 2017 1:14 PM
To: Lapinski, Mary-Sumpter (HHS/IOS)
Cc: Baker, Rebecca (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]
Subject: RE: Pressing need to discuss four items with you

Thanks, Mary-Sumpter. If we want good coverage of this event in the press, late morning is a lot better than early afternoon. Any chance of that?

Francis

From: Lapinski, Mary-Sumpter (HHS/IOS) (b) (6)
Sent: Friday, September 22, 2017 12:57 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Myles, Renate (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6)
Subject: RE: Pressing need to discuss four items with you

Thank you! Scheduling says he can do 10/12 1:30p-2:30p – that work? (I will go ahead and have them hold it, since I'm an optimist.)

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Friday, September 22, 2017 11:39 AM
To: Lapinski, Mary-Sumpter (HHS/IOS)
Cc: Baker, Rebecca (NIH/OD) [E]; Burklow, John (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]
Subject: RE: Pressing need to discuss four items with you

Hi Mary-Sumpter,

Actually the week of October 9 would be a lot better – the participating companies need a little prep time to arrange for their CEOs or other high ranking officials to appear at the Press Conference. October 10 or 12 are looking particularly good. Can you explore that with the scheduling team?

We are imagining a late morning one hour event, at the National Press Club.

Francis

From: Lapinski, Mary-Sumpter (HHS/IOS) [REDACTED] (b) (6)
Sent: Friday, September 22, 2017 11:05 AM
To: Collins, Francis (NIH/OD) [E] [REDACTED] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] [REDACTED] (b) (6)
Subject: RE: Pressing need to discuss four items with you

Dear Francis,

Happy Friday!

We are looking at week of Oct 2 for PACT. His scheduling team is asking how much time you're requesting of Sec. Price?

Thanks,
Mary-Sumpter

From: Wholley, David (FNIH) [T]
Sent: Mon, 6 Nov 2017 14:03:31 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: RE: PACT EC

Francis, will do, and I will let Jim know you are starting out as co-chair. FYI I would imagine EC would not meet before early December—we'll need that long to come up with a final research plan that the delegates to the F2F agree to, not to mention electing the company reps. I assume the rest of the structure as I have described it suits you.

From: Collins, Francis (NIH/OD) [E]
Sent: Saturday, November 4, 2017 4:04 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: FW: PACT EC

Hi David,

See below. Ideally I would think that Ned Sharpless would be the right NIH co-chair for the PACT EC. But his need for divestments and recusals may make this complicated for a while. For now, maybe best to make me co-chair (but I will hand off to Ned when he is clear). Definitely put Jim Doroshow on the EC.

FC

From: Tabak, Lawrence (NIH/OD) [E]
Sent: Friday, November 03, 2017 1:01 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: Re: PACT EC

(b) (5)

--

From: Francis Collins (b) (6)
Date: Friday, November 3, 2017 at 12:58 PM
To: "Tabak, Lawrence (NIH/OD) [E]" (b) (6)
Subject: FW: PACT EC

See below. (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Friday, November 03, 2017 11:50 AM

To: Collins, Francis (NIH/OD) [E] (b) (6)

Subject: PACT EC

Hi Francis –

Back to PACT for a moment. Stacey Adam and I met with Jim Doroshow and his NCI team last night to start getting set for the face to face meeting we are holding on November 16 to finalize the detailed research plan for PACT (as we did with the AMP initiatives). Among the topics tackled was governance, and NCI is working on suggested representatives for the JSC.

(b) (5)

Thanks, David

We've moved! Please find our new address below.

David Wholley

Director, Research Partnerships

Foundation for the National Institutes of Health

(301) 594-6343

fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Tue, 26 Sep 2017 11:18:05 +0000
To: Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: Re: PACT follow-up

(b) (4)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 6:34 AM
To: Wholley, David (FNIH) [T]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: PACT follow-up

(b) (4)

From: Wholley, David (FNIH) [T]
Sent: Monday, September 25, 2017 12:08 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: FW: PACT follow-up

(b) (4)

(b) (4) Please let me know any other thoughts...

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: (b) (4)
Sent: Monday, September 25, 2017 11:16 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: (b) (4); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: PACT follow-up

Hi David,

(b) (4)



From: Wholley, David (FNIH) [T]
Sent: Tue, 26 Sep 2017 14:15:09 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: RE: PACT follow-up

sure

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 10:12 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: RE: PACT follow-up

(b) (4)

FC

From: Wholley, David (FNIH) [T]
Sent: Tuesday, September 26, 2017 7:18 AM
To: Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Re: PACT follow-up

(b) (4)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 6:34 AM
To: Wholley, David (FNIH) [T]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: PACT follow-up

(b) (4)

From: Wholley, David (FNIH) [T]
Sent: Monday, September 25, 2017 12:08 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: FW: PACT follow-up

(b) (4)

(b) (4) Please let me know any other thoughts...

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
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From: (b) (4)
Sent: Monday, September 25, 2017 11:16 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: (b) (4) Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: PACT follow-up

Hi David,

(b) (4)

From: Wholley, David (FNIH) [T]
Sent: Tue, 5 Sep 2017 12:24:19 +0000
To: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]
Subject: Re: slide set for Thursday

I'm happy to take a look once Rebecca has pulled together.
Sent from my BlackBerry 10 smartphone.

From: Baker, Rebecca (NIH/OD) [E]
Sent: Tuesday, September 5, 2017 7:53 AM
To: Wolinetz, Carrie (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Wholley, David (FNIH) [T]
Subject: Re: slide set for Thursday

Happy to help! I could pull a structure from previously generated materials, made with Walter's input, to organize discussion.
Rebecca

On Sep 5, 2017, at 7:44 AM, Wolinetz, Carrie (NIH/OD) [E] (b) (6) wrote:

Francis,
I think in addition to asking Walter to work with Rebecca you should let our exactly what you want to see - perhaps a slightly expanded version of what you've outlined below? I think pretty explicit direction is going to be necessary to get these into shape. Cheers, Carrie
Carrie D. Wolinetz, Ph.D.
Acting Chief of Staff and
Associate Director for Science Policy
Office of the Director
National Institutes of Health
(b) (6)

----- Original message -----

From: "Collins, Francis (NIH/OD) [E]" (b) (6)
Date: 9/5/17 7:20 AM (GMT-05:00)
To: "Baker, Rebecca (NIH/OD) [E]" (b) (6) "Wolinetz, Carrie (NIH/OD) [E]" (b) (6) "Tabak, Lawrence (NIH/OD) [E]" (b) (6)
"Wholley, David (FNIH) [T]" <dwholley@fnihi.org>
Subject: RE: slide set for Thursday

Oh dear. This slide set is a disaster. I'm on travel until late today – shall I encourage Walter to get advice from Rebecca this morning, and try to turn this into something more appropriate for Sept. 7? The goal should be to set up a discussion about the main components of a potential PPP that emerged from workshops 2 and 3 (but especially 2): accelerating drugs in current pipeline, biomarkers, data sharing, pain-o-meter, trial network.

FC

From: Koroshetz, Walter (NIH/NINDS) [E]
Sent: Monday, September 04, 2017 9:31 PM
To: Baker, Rebecca (NIH/OD) [E] (b) (6)
Cc: Collins, Francis (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E]
(b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Volkow, Nora
(NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6)
Subject: slide set for Thursday

Please take a look if you can and comment.
Suspect will want to have uniform template??
Thanks
Walter

Walter J. Koroshetz, M.D.
Director, National Institute of Neurological Disorders and Stroke

From: Wholley, David (FNIH) [T]
Sent: Fri, 6 Oct 2017 19:26:54 +0000
To: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]
Subject: Re: Speaking invitation: PACT press conference October 12

(b) (5)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Friday, October 6, 2017 2:00 PM
To: Wholley, David (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Subject: FW: Speaking invitation: PACT press conference October 12

(b) (5)

From: Sandra Horning [mailto:horning.sandra@gene.com]
Sent: Friday, October 06, 2017 1:56 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Alanna Lyons <lyons.alanna@gene.com>; James Larkin <larkin.james@gene.com>
Subject: Re: Speaking invitation: PACT press conference October 12

Dear Francis,

I appreciate the honor of the invitation to participate in next week's PACT press conference but I have a long standing commitment with my team, some of whom are coming from Europe, that conflicts with that date.

I do hope you have a highly successful event and trust that among the multiple industry partners that you will readily identify a representative speaker.

All the best and thank you for your consideration,
Sandra

On Oct 6, 2017, at 9:39 AM, Collins, Francis (NIH/OD) [E] (b) (6) wrote:

Dear Sandra,

Many thanks to you and your colleagues at Genentech for your contributions to the design of PACT, and for agreeing to take the next step with us in this important and exciting partnership.

We are assembling the agenda for the event next week announcing the partnership, and would like to invite you to say a few words representing the 9 private sector partners in PACT (Novartis has also just joined). We would set aside approximately 5-7 minutes for your remarks, and would be pleased to assist you in any way as you prepared for the event. Other speakers will likely include the Acting HHS Secretary, myself, Acting NCI Director Douglas Lowy, and a patient who has benefitted from chemotherapy.

With apologies for the last minute request, please let me know at your earliest convenience whether you'd be interested in speaking next week.

Thank you again,

Francis

From: Collins, Francis (NIH/OD) [E]

Sent: Tuesday, October 3, 2017 9:29 PM

To: michael.severino@abbvie.com; thomas.hudson@abbvie.com; norbert.kraut@boehringer-ingenlheim.com; thomas.lynch@bms.com; rvessey@celgene.com; horning.sandra@gene.com; perez.edith@gene.com; patrick.5.vallance@gsk.com; axel.x.hoos@gsk.com; Mikael.Dolsten@pfizer.com; paul.rejto@pfizer.com; robert.abraham@pfizer.com; PStoffe4@its.inj.com; plebowit@its.inj.com

Cc: Myles, Renate (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshov, James (NIH/NCI) [E] (b) (6)

Subject: Invitation to PACT press conference October 12

Dear Colleagues:

We've been working together for more than a year to develop the Partnership to Accelerate Cancer Therapies (PACT) and I am excited to invite you to participate with HHS, NIH, NCI, FDA, and the Foundation for the NIH in a press conference at the National Press Club on Thursday, Oct. 12 at 10:00 a.m. ET to launch this important new partnership. The NPC is located at 528 14th St. NW, Washington, D.C. We have reserved a green room for the entire day (Zenger Room) and will hold a "pre-event" meeting in this room at 9:15 a.m., with the press conference beginning promptly at 10:00 a.m. ET in the Fourth Estate Room.

Given recent changes in HHS leadership, we are not quite sure who will serve as Departmental convener of the press conference, but it is likely to be Acting Secretary Don Wright. Following that, brief remarks will be made by myself, potentially NCI Director Ned Sharpless, whom we hope to have officially on

board by then, an industry representative, and a patient who has benefited from cancer immunotherapy. There is also a possibility that Reed Cordish, the White House Assistant to the President for Intragovernmental and Technology Initiatives, will join the event.

We hope to leave a good amount of time for questions from reporters. We will have the front rows reserved for speakers, members of the media, and yourselves. Also, after the event, reporters may want to speak with you, so I hope you can stay around for a bit after the formal meeting. Seating is limited, so please limit your organization's participation to yourself (or a surrogate) plus one.

We will likely have event itinerary and materials to share with you next week. Please provide to (b) (6) the name and contact information for your communications director, so that John Burklow and Renate Myles on our NIH Communications staff can coordinate with them on materials and quotes to include in our media kits.

Best regards, and thanks for your support of this groundbreaking initiative,
Francis

From: Wholley, David (FNIH) [T]
Sent: Fri, 6 Oct 2017 20:28:49 +0000
To: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]
Subject: RE: Speaking invitation: PACT press conference October 12

(b) (5)

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Collins, Francis (NIH/OD) [E]
Sent: Friday, October 06, 2017 4:24 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Myles, Renate (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: Speaking invitation: PACT press conference October 12

(b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Friday, October 06, 2017 3:27 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshow, James (NIH/NCI) [E] (b) (6); Myles, Renate (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Re: Speaking invitation: PACT press conference October 12

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]

Sent: Friday, October 6, 2017 2:00 PM

To: Wholley, David (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshov, James (NIH/NCI) [E]; Myles, Renate (NIH/OD) [E]; Burklow, John (NIH/OD) [E]

Subject: FW: Speaking invitation: PACT press conference October 12

(b) (5)

From: Sandra Horning [mailto:horning.sandra@gene.com]

Sent: Friday, October 06, 2017 1:56 PM

To: Collins, Francis (NIH/OD) [E] (b) (6)

Cc: Alanna Lyons <lyons.alanna@gene.com>; James Larkin <larkin.james@gene.com>

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Thank you again,

Francis

From: Collins, Francis (NIH/OD) [E]

Sent: Tuesday, October 3, 2017 9:29 PM

To: michael.severino@abbvie.com; thomas.hudson@abbvie.com; norbert.kraut@boehringer-ingelheim.com; thomas.lynnch@bms.com; rvessey@celgene.com; horning.sandra@gene.com; perez.edit.h@gene.com; patrick.5.vallance@gsk.com; axel.x.hoos@gsk.com; Mikael.Dolsten@pfizer.com; paul.rejt.o@pfizer.com; robert.abraham@pfizer.com; PStoffe4@its.inj.com; plebowit@its.inj.com

Cc: Myles, Renate (NIH/OD) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Lowy, Douglas (NIH/NCI) [E] (b) (6); Doroshov, James (NIH/NCI) [E] (b) (6)

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Best regards, and thanks for your support of this groundbreaking initiative,
Francis

From: Wholley, David (FNIH) [T]
Sent: Mon, 18 Sep 2017 11:46:14 +0000
To: Chin, Bill; Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]
Subject: Re: Successes of PPPs

I second all of these. Within the BC, ISPY-2 is a particularly well-known project.

Sent from my BlackBerry 10 smartphone.

Original Message

From: Chin, Bill
Sent: Sunday, September 17, 2017 7:52 PM
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wholley, David (FNIH) [T]
Subject: Re: Successes of PPPs

Thanks, Francis. Very helpful. See you tomorrow. Bill

Sent from my iPhone

> On Sep 17, 2017, at 2:30 PM, Collins, Francis (NIH/OD) [E] (b) (6) wrote:
>
> Hi Bill,
>
> Not sure whether David might have already responded to you, but I would list:
> 1) Osteoarthritis initiative: www.niams.nih.gov/Funding/Funded_Research/Osteoarthritis_Initiative/
> 2) Alzheimer's Disease Neuroimaging (ADNI) consortium: <http://www.adni-info.org/>
> 3) Biomarkers consortium: fnih.org/what-we-do/biomarkers-consortium
> 4) NCATS drug repurposing program: ncats.nih.gov/ntu
> 5) AMP -- T2D, Alzheimer's, RA/SLE, and now Parkinson's: www.nih.gov/research-training/accelerating-medicines-partnership-amp
> 6) Under construction but ready to announce quite soon -- PACT (Partnership for Advancing Cancer Therapies)
>
> Francis
>
>
> -----Original Message-----
> From: Chin, Bill [mailto:Chin@phrma.org]
> Sent: Saturday, September 16, 2017 1:49 PM
> To: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Collins, Francis (NIH/OD) [E] (b) (6)
> Cc: Baker, Rebecca (NIH/OD) [E] (b) (6)
> Subject: Successes of PPPs
>
> David and Francis, Am preparing Steve with some TPs on examples of PPP successes. What would you consider prime ones from AMP, FNIH or elsewhere? Thanks. Bill
>
> Sent from my iPhone

From: Wholley, David (FNIH) [T]
Sent: Thu, 21 Dec 2017 20:27:33 +0000
To: Moscicki, Richard
Subject: RE: Summary of the summit meeting

Rich, the only change I noticed was breaking out the AMP and PACT stuff into a separate section. I noticed that there is a typo in "Partnerships" in header for page 4, but otherwise it looks fine to me. Thanks, David

From: Moscicki, Richard [mailto:rmoscicki@phrma.org]
Sent: Thursday, December 21, 2017 2:36 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: Summary of the summit meeting

Hi David, attached are some minor changes in the document. If you are ok with them, we will send to BMAC after legal review. Rich.

From: Wholley, David (FNIH) [T]
Sent: Tue, 14 Nov 2017 00:37:43 +0000
To: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Stein, Jack (NIH/NIDA) [E]; Porter, Linda (NIH/NINDS) [E]
Subject: RE: TIME SENSITIVE REQUEST FROM ACTING SECRETARY

(b) (4), (b) (5)

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, November 13, 2017 7:22 PM
To: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: TIME SENSITIVE REQUEST FROM ACTING SECRETARY

Hi all,

In my regular 1:1 with Acting Secretary Hargan at the end of today, we discussed the research needs/opportunities in opioids. We had sent the same document to him as a pre-read that was shared with the Hill last week (attached), which lists a (b) (4), (b) (5), if we are really pulling out all the stops. I told him about our deep concerns about where this would be coming from, given that the Administration had not promised anything at the time of the President's opioid speech. I told him that I thought companies might be willing to contribute something in the range of

(b) (4), (b) (5)

He wanted to know what NIH could come up with by prioritizing.

(b) (4), (b) (5)


(b) (4), (b) (5)

I told him that we had been getting calls from the Congress, and that there was a reasonable possibility they might provide some funding – referencing the Shaheen et al. letter which asked the POTUS to tell them where the needs were.

It turns out that he is meeting with OMB tomorrow afternoon, and is prepared to make a pitch to them that the Administration ought to act. What he wants from us by midday tomorrow (sooner is better), with cc's to Mary-Sumpter Lapinski, Charles Keckler (who sat in on the meeting), and Jen Moughalian (whom he forgot, and had to be reminded by MSL – interesting) – was a range of what we think might be possible for next year. He didn't specifically ask about the outyears, and I'm much less sanguine about those.

I would think the formula might look something like this:

(b) (4), (b) (5)



(b) (5) Please respond (if possible) this evening. I may need Rebecca's help in turning this into a response to Hargan.

FC

From: Wholley, David (FNIH) [T]
Sent: Tue, 14 Nov 2017 02:18:00 +0000
To: Tabak, Lawrence (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Stein, Jack (NIH/NIDA) [E]; Porter, Linda (NIH/NINDS) [E]
Subject: RE: TIME SENSITIVE REQUEST FROM ACTING SECRETARY

(b) (5)

From: Tabak, Lawrence (NIH/OD) [E]
Sent: Monday, November 13, 2017 9:17 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: Re: TIME SENSITIVE REQUEST FROM ACTING SECRETARY

Francis,

(b) (4), (b) (5)

Larry

--

From: Francis Collins (b) (6)
Date: Monday, November 13, 2017 at 7:22 PM
To: "Baker, Rebecca (NIH/OD) [E]" (b) (6), "Wolinetz, Carrie (NIH/OD) [E]" (b) (6), "Tabak, Lawrence (NIH/OD) [E]" (b) (6), "Volkow, Nora (NIH/NIDA) [E]" (b) (6), "Koroshetz, Walter (NIH/NINDS) [E]" (b) (6), "Stein, Jack (NIH/NIDA) [E]" (b) (6), "Porter, Linda (NIH/NINDS) [E]" (b) (6), "Wholley, David (FNIH) [T]" <dwholley@fnih.org>
Subject: TIME SENSITIVE REQUEST FROM ACTING SECRETARY

Hi all,

In my regular 1:1 with Acting Secretary Hargan at the end of today, we discussed the research needs/opportunities in opioids. We had sent the same document to him as a pre-read that was shared with the Hill last week (attached), which lists a (b) (4), (b) (5), if we are really pulling out all the stops. I told him about our deep concerns about where this would be coming from, given that the Administration had not promised anything at the time of the President's opioid speech. I told him that I thought companies might be willing to contribute something in the range of

(b) (4), (b) (5)

He wanted to know what NIH could come up with by prioritizing.

(b) (4), (b) (5)

(b) (4), (b) (5)

I told him that we had been getting calls from the Congress, and that there was a reasonable possibility they might provide some funding – referencing the Shaheen et al. letter which asked the POTUS to tell them where the needs were.

It turns out that he is meeting with OMB tomorrow afternoon, and is prepared to make a pitch to them that the Administration ought to act. What he wants from us by midday tomorrow (sooner is better), with cc's to Mary-Sumpter Lapinski, Charles Keckler (who sat in on the meeting), and Jen Moughalian (whom he forgot, and had to be reminded by MSL – interesting) – was a range of what we think might be possible for next year. He didn't specifically ask about the outyears, and I'm much less sanguine about those.

I would think the formula might look something like this:

(b) (4), (b) (5)

(b) (5) Please respond (if possible) this evening. I may need Rebecca's help in turning this into a response to Hargan.

FC

From: Wholley, David (FNIH) [T]
Sent: Tue, 19 Sep 2017 13:27:46 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: RE: Today's Meeting with Governor Christie

Hi Francis,

I am not sure how many companies we expect will now be interested in joining in the opioids effort (and for how many separate projects), [REDACTED] (b) (4), (b) (5)

We paid for Parkinson's development out of AMP funds. For PACT you kicked in \$150K and we raised an additional \$300K from companies. [REDACTED] (b) (4), (b) (5)

(b) (4), (b) (5)

Can you please advise how you'd like to cover this? Thanks

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnihi.org

Learn more about the FNIH in our 2016 Annual Report: fnihi.org/AnnualReport.

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 19, 2017 4:14 AM
To: Chin, Bill <Chin@phrma.org>
Cc: Volkow, Nora (NIH/NIDA) [E] [REDACTED] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] [REDACTED] (b) (6); Baker, Rebecca (NIH/OD) [E] [REDACTED] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Wolinetz, Carrie (NIH/OD) [E] [REDACTED] (b) (6); Tabak, Lawrence (NIH/OD) [E] [REDACTED] (b) (6)
Subject: RE: Today's Meeting with Governor Christie

Hi Bill,

I agree that the meeting yesterday went really well. I spoke with Steve Ubl afterward -- and he and I thought that a joint letter from PhRMA and NIH to the CEOs of all of the companies that had been part of the discussion up until now would be the next step. The letter could include the 2-pager that summarizes the plan, and would ask each company to make a commitment to take part in the next step -- to develop a specific work plan for projects 1 and 2. [REDACTED] (b) (4)

[REDACTED] (b) (4) We would ask each company to name a point person to work with NIH and FNIH on the plan, and would ask that that person make this their number one priority so that meetings can be set up expeditiously. The goal would be a fully detailed plan in place by the end of 2017, including specific actionable goals, deliverables, milestones, Go NoGo decision points, and budget.

[REDACTED] (b) (6) but we will move forward quickly with this plan.

Francis

-----Original Message-----

From: Chin, Bill [<mailto:Chin@phrma.org>]

Sent: Monday, September 18, 2017 2:40 PM

To: Collins, Francis (NIH/OD) [E] (b) (6)

Cc: Volkow, Nora (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E]

(b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6)

Subject: Today's Meeting with Governor Christie

Francis, As we discussed, I think the meeting went very well with good representation from the companies and active engagement from the CEOs. Our next step is a memo to our Board with the request to "assign" an accountable person in each company to help provide the details for these PPPs. I'll be away this week but will get the ball rolling. Thank you all and best wishes. Bill

Sent from my iPhone

From: Wholley, David (FNIH) [T]
Sent: Tue, 19 Sep 2017 16:05:00 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: RE: Today's Meeting with Governor Christie

Hi Francis,

(b) (5)

Thanks--

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-----Original Message-----

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 19, 2017 9:45 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: RE: Today's Meeting with Governor Christie

(b) (4), (b) (5)

-----Original Message-----

From: Wholley, David (FNIH) [T]
Sent: Tuesday, September 19, 2017 9:28 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: RE: Today's Meeting with Governor Christie

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(b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wholley, David (FNIH)
[T] <dwholley@fnih.org>; Wolinetz, Carrie (NIH/OD) [E] (b) (6); Tabak, Lawrence
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(b) (4)
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Cc: Volkow, Nora (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E]
(b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6)
Subject: Today's Meeting with Governor Christie

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Sent from my iPhone

From: Wholley, David (FNIH) [T]
Sent: Thu, 7 Sep 2017 01:55:25 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: Re: Tomorrow's Call

Francis-- thanks for copying me on your reply. [REDACTED] (b) (4), (b) (5)

[REDACTED] (b) (4), (b) (5)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, September 6, 2017 7:38 PM
To: Chin, Bill
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Wholley, David (FNIH) [T]
Subject: RE: Tomorrow's Call

Hi Bill,

It would be great if you would prime some of the participants for tomorrow's telecon.

As for Sept. 18, you have seen 100% of what I know – hopefully there will be more info forthcoming from Amy Cradic soon.

Best, Francis

From: Chin, Bill [mailto:Chin@phrma.org]
Sent: Wednesday, September 06, 2017 7:36 PM
To: Collins, Francis (NIH/OD) [E] [REDACTED] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] [REDACTED] (b) (6); Wolinetz, Carrie (NIH/OD) [E]
[REDACTED] (b) (6)
Subject: Re: Tomorrow's Call

Thanks, Francis. Re: Discussion. I can help, too. [REDACTED] (b) (4)

[REDACTED] Re: Governor Christie—This is getting a bit clearer although 2 hours is a long time without a specific agenda, even if part of it will involve your presentation of a proposed PPP framework. Also, who will be the “attendees” that will soon be disclosed? If they include some of our CEOs, it would be good for me to help prepare them and assure them that they will not be brow-beaten, for instance. Bill

On Sep 6, 2017, at 7:07 PM, Collins, Francis (NIH/OD) [E] [REDACTED] (b) (6) wrote:

Hi Bill,

I totally agree with the importance of making tomorrow's telecon a collaborative discussion – and I am also worried that the initial presentations, while intended to prime the pump, might make it appear that the PPP is already completely baked. I will do my best in the opening remarks to make it clear that is not the case, and also to emphasize that the ideas being put forward by Nora and Walter are not just NIH ideas, they are the outcome of the three workshops that had heavy industry participation.

David Wholley and I are also plotting ideas about how to call on industry folks to get the discussion going, in case there is awkward silence when we get to the Discussion section.

As for Sept. 18, I just got an e-mail from Amy Cradic (Christie's chief of staff). Here's what she said:

Dr. Collins – the meeting will be held between 11 am and 1 pm. We can pick you up at the Trenton Train Station. Let me know how many people will be with you. I hope to send a list of attendees soon. I've copied Mary Beth to work with Gretchen on setting up a call so we can discuss agenda - thx

War Memorial – Woodrow Wilson Board Room,
1 Memorial Drive, Trenton, NJ 08608
Parking for guests will be in Lot A and Lot B adjacent to the War Memorial.

Best, Francis

From: Chin, Bill [<mailto:Chin@phrma.org>]
Sent: Wednesday, September 06, 2017 4:32 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: Tomorrow's Call

Francis, We look forward to tomorrow's call. As much as possible though, could we make this TC a true collaborative discussion—one involving both NIH/FDA and industry? I'm concerned that the quantity and tenor of the slides might make it look like that the PPP effort is solely a NIH initiative and not truly a partnership. Sorry to be so direct. I'm available all evening and very early morning if you need to speak to me (b) (6). Bill PS I'm still concerned about the lack of clarity about the 9/18 Christie meeting.

From: Wholley, David (FNIH) [T]
Sent: Thu, 13 Jul 2017 16:52:29 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: UPDATE RE: urgent phone calls to set up - (b) (4), (b) (5)

Great. (b) (4), (b) (5) as it will realistically be 4Q before redesign is completed, NCI does awards for the RFAs (this is my understanding) and this thing really gets off the ground. (b) (4), (b) (5)

(b) (4), (b) (5) But we'll have to cross that bridge when we come to it.

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fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, July 13, 2017 4:37 PM
To: Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Re: UPDATE RE: urgent phone calls to set up (b) (4), (b) (5)

Good call with (b) (4), (b) (5). He won't be at the meeting tomorrow but thinks (b) (6) will be successful (b) (4), (b) (5)

Sent from my iPhone

On Jul 13, 2017, at 4:05 PM, Wood, Gretchen (NIH/OD) [E] (b) (6) wrote:

Update:

Francis is speaking with (b) (4), (b) (5) at 4:15 PM (b) (6) and (b) (6) will dial FC's iPhone at 4:45 PM. (4)

From: Wholley, David (FNIH) [T]
Sent: Thursday, July 13, 2017 12:47 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>

(b) (4), (b) (5)

Subject: RE: urgent phone calls to set up -
Importance: High

Francis, as promised, here is the summary background you requested:

(b) (4), (b) (5)

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From: Collins, Francis (NIH/OD) [E]

Sent: Thursday, July 13, 2017 12:05 PM

To: Wood, Gretchen (NIH/OD) [E] (b) (6)

Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6)

Wolinetz, Carrie (NIH/OD) [E] (b) (6) Adam, Stacey (FNIH) [T] <sadam@fnih.org>

Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)

David/Stacey might be able to help with phone numbers that would get through.

The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Mon, 2 Oct 2017 18:58:59 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]
Subject: Re: Update on PACT?

(b) (4), (b) (5)

Thanks

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, October 2, 2017 2:48 PM
To: Wholley, David (FNIH) [T]
Cc: Adam, Stacey (FNIH) [T]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]
Subject: RE: Update on PACT?

(b) (4), (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Monday, October 02, 2017 2:08 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Wolinetz, Carrie (NIH/OD) [E]
(b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Myles, Renate (NIH/OD) [E] (b) (6)
Subject: FW: Update on PACT?

(b) (4), (b) (5)

Thanks, David

David Wholley
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From: (b) (4)
Sent: Monday, October 02, 2017 12:34 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: (b) (4); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: Update on PACT?

David,

(b) (4)

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnih.org>]
Sent: Monday, October 02, 2017 9:45 AM
To: (b) (4)
Cc: (b) (4); Adam, Stacey (FNIH) [T]
Subject: RE: Update on PACT?

(b) (4)

NIH is moving forward with their communications and announcement plan for the 12th, and are asking me for status.
Thanks,
David

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fnih.org

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From: (b) (4)
Sent: Wednesday, September 27, 2017 3:28 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: (b) (4); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: Update on PACT?

David,

I apologize for the delays.

(b) (4)

(b) (4)

From: Wholley, David (FNIH) [T] [mailto:dwholley@fnih.org]

Sent: Tuesday, September 26, 2017 4:20 PM

To: (b) (4)

Cc: (b) (4); Adam, Stacey (FNIH) [T]

Subject: RE: Update on PACT?

(b) (4)

The announcement of the launch of the Partnership to Advance Cancer Therapies (PACT) is almost certainly going to be on October 12, at the National Press Club. (b) (4)

Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: (b) (4)

Sent: Monday, September 18, 2017 5:49 PM

To: Wholley, David (FNIH) [T] <dwholley@fnih.org>

Cc: (b) (4); Adam, Stacey (FNIH) [T] <sadam@fnih.org>

Subject: Re: Update on PACT?

David,

Sorry for the delayed reply. (b) (6)

(b) (4)

Sent from my iPhone

On Sep 15, 2017, at 2:47 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

(b) (4)

Please let me know, or any additional information I can supply you.
Best regards,

David Wholley

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Friday, September 08, 2017 10:21 AM
To: (b) (4)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Update on PACT?

(b) (4)

(b) (4) Thank you,

David Wholley

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
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From: Wholley, David (FNIH) [T]
Sent: Mon, 2 Oct 2017 20:08:16 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: Re: Update on PACT?

(b) (4), (b) (5)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Monday, October 2, 2017 3:00 PM
To: Wholley, David (FNIH) [T]
Cc: Adam, Stacey (FNIH) [T]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Myles, Renate (NIH/OD) [E]
Subject: RE: Update on PACT?

(b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Monday, October 02, 2017 2:59 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>; Wolinetz, Carrie (NIH/OD) [E]
(b) (6); Baker, Rebecca (NIH/OD) (b) (6); Myles, Renate (NIH/OD) [E] (b) (6)
Subject: Re: Update on PACT?

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Subject: RE: Update on PACT?

David,

(b) (4)

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From: [REDACTED] (b) (4)
Sent: Wednesday, September 27, 2017 3:28 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: [REDACTED] (b) (4); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: Update on PACT?

David,

I apologize for the delays. [REDACTED] (b) (4)

From: Wholley, David (FNIH) [T] [<mailto:dwholley@fnih.org>]
Sent: Tuesday, September 26, 2017 4:20 PM
To: [REDACTED] (b) (4)
Cc: [REDACTED] (b) (4); Adam, Stacey (FNIH) [T]
Subject: RE: Update on PACT?

[REDACTED] (b) (4)

The announcement of the launch of the Partnership to Advance Cancer Therapies (PACT) is almost certainly going to be on October 12, at the National Press Club. [REDACTED] (b) (4)

Thanks, David

David Wholley
Director, Research Partnerships
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Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: [REDACTED] (b) (4)
Sent: Monday, September 18, 2017 5:49 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: [REDACTED] (b) (4); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Re: Update on PACT?

David,

Sorry for the delayed reply.

(b) (6)

(b) (4)

Sent from my iPhone

On Sep 15, 2017, at 2:47 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

H (b) (4):

(b) (4)

Best regards,
David Wholley

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
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fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Friday, September 08, 2017 10:21 AM
To: (b) (4)
Cc: Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Update on PACT?

(b) (4)

(b) (4) Thank you,

David Wholley

David Wholley
Director, Research Partnerships
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fnih.org

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From: Wholley, David (FNIH) [T]
Sent: Fri, 10 Nov 2017 17:08:11 +0000
To: Baker, Rebecca (NIH/OD) [E]
Cc: Collins, Francis (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]
Subject: RE: quick review of draft note reserving 12-13 Dec

I have a concern with the 12-13 date, Rebecca. I am trying to determine if the room available—the only one we are able to find—will be big enough to accommodate all the people now on the list to come, and if not what a tenable solution would be around that time. I understand you are anxious to get this out, but I would ask that you please hold off until we are further confirmed on this.

From: Baker, Rebecca (NIH/OD) [E]
Sent: Friday, November 10, 2017 11:40 AM
To: Biarnes, Michael (FNIH) [T] <mbiarnes@fnih.org>; Wholley, David (FNIH) [T] <dwholley@fnih.org>
Subject: quick review of draft note reserving 12-13 Dec

Hi David and Michael,

Francis would like to send out today the note we discussed at yesterday's meeting, identifying the priority areas and informing the potential partners of the 12-13 date. Do you have any concerns with the attached draft?

Thanks for letting me know ASAP.

Best,
Rebecca

From: Wholley, David (FNIH) [T]
Sent: Thu, 7 Sep 2017 21:26:27 +0000
To: Baker, Rebecca (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Stein, Jack (NIH/NIDA) [E]; Porter, Linda (NIH/NINDS) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Schwetz, Tara (NIH/OD) [E]
Subject: Re: QUICK TURNAROUND REVIEW: Agenda for 9-11 meeting of PhRMA BMAC

I will attend in person.

Sent from my BlackBerry 10 smartphone.

From: Baker, Rebecca (NIH/OD) [E]
Sent: Thursday, September 7, 2017 5:14 PM
To: Volkow, Nora (NIH/NIDA) [E]; Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Stein, Jack (NIH/NIDA) [E]; Porter, Linda (NIH/NINDS) [E]; Wholley, David (FNIH) [T]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Schwetz, Tara (NIH/OD) [E]
Subject: QUICK TURNAROUND REVIEW: Agenda for 9-11 meeting of PhRMA BMAC

Good afternoon,

Bill Chin has developed the attached agenda for Monday 9-11-2017's meeting of the Biomedical Advisory Council of PhRMA.

I have let him know that Ellen Fields will be representing FDA, but do other have proposed edits or revisions?

He has requested any comments tonight.

Also, could you please confirm your participation in the 9-11-2017 meeting, specifying in person or by phone, so that I can provide this information to PhRMA?

Thank you,
Rebecca

From: Wholley, David (FNIH) [T]
Sent: Wed, 27 Sep 2017 20:31:22 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: RE: really glad you are back!

Hi Francis,

I spoke to Bill. He is going to sign an agreement to give us \$100K immediately, (b) (4), (b) (5)

(b) (4), (b) (5)

David

David Wholley
Director, Research Partnerships
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From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 2:49 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E]
(b) (6)
Subject: FW: really glad you are back!

FYI

From: Chin, Bill [<mailto:Chin@phrma.org>]
Sent: Tuesday, September 26, 2017 2:17 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: RE: really glad you are back!

Francis, Thanks. I/we am/are fully committed to making this work (b) (4)

(b) (4)

(b) (4) he hat. Bill

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Tuesday, September 26, 2017 1:57 PM
To: Chin, Bill
Subject: really glad you are back!

Hi Bill,

Glad you have returned and we were able to make a plan quickly by phone. It was surprisingly difficult to get these issues resolved without your presence, which makes me nervous about 2018.

(b) (4)

Best, Francis

From: Wholley, David (FNIH) [T]
Sent: Wed, 27 Sep 2017 15:23:29 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: RE: really glad you are back!

Hi Francis -

(b) (4), (b) (5)

Thanks, David

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From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 2:49 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E]
(b) (6)
Subject: FW: really glad you are back!

FYI

From: Chin, Bill [<mailto:Chin@phrma.org>]
Sent: Tuesday, September 26, 2017 2:17 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: RE: really glad you are back!

Francis, Thanks. I/we am/are fully committed to making this work

(b) (4)

(b) (4)

(b) (4) Bill

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Tuesday, September 26, 2017 1:57 PM
To: Chin, Bill
Subject: really glad you are back!

Hi Bill,

Glad you have returned and we were able to make a plan quickly by phone. It was surprisingly difficult to get these issues resolved without your presence, which makes me nervous about 2018.

(b) (4)

Best, Francis

From: Wholley, David (FNIH) [T]
Sent: Wed, 27 Sep 2017 01:49:11 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: Re: really glad you are back!

(b) (4), (b) (5)

(b) (4), (b) (5) Thanks for letting me know.

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 2:49 PM
To: Wholley, David (FNIH) [T]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: FW: really glad you are back!

FYI

From: Chin, Bill [mailto:Chin@phrma.org]
Sent: Tuesday, September 26, 2017 2:17 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: RE: really glad you are back!

Francis, Thanks. I/we am/are fully committed to making this work

(b) (4)

(b) (4)

(b) (4) Bill

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Tuesday, September 26, 2017 1:57 PM
To: Chin, Bill
Subject: really glad you are back!

Hi Bill,

Glad you have returned and we were able to make a plan quickly by phone. It was surprisingly difficult to get these issues resolved without your presence, which makes me nervous about 2018.

(b) (4)

Best, Francis

From: Wholley, David (FNIH) [T]
Sent: Wed, 27 Sep 2017 22:18:25 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: RE: really glad you are back!

Francis<

(b) (4), (b) (5)

David
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From: Collins, Francis (NIH/OD) [E]
Sent: Wednesday, September 27, 2017 4:37 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E]
(b) (6)
Subject: RE: really glad you are back!

(b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Wednesday, September 27, 2017 4:31 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E]
(b) (6)
Subject: RE: really glad you are back!

Hi Francis,

I spoke to Bill. He is going to sign an agreement to give us \$100K immediately,

(b) (4), (b) (5)

(b) (4), (b) (5)

David

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From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, September 26, 2017 2:49 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E]
(b) (6)
Subject: FW: really glad you are back!

FYI

From: Chin, Bill [<mailto:Chin@phrma.org>]
Sent: Tuesday, September 26, 2017 2:17 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Subject: RE: really glad you are back!

Francis, Thanks. I/we am/are fully committed to making this work (b) (4)
(b) (4)
(b) (4) Bill

From: Collins, Francis (NIH/OD) [E] (b) (6)
Sent: Tuesday, September 26, 2017 1:57 PM
To: Chin, Bill
Subject: really glad you are back!

Hi Bill,

Glad you have returned and we were able to make a plan quickly by phone. It was surprisingly difficult to get these issues resolved without your presence, which makes me nervous about 2018.

(b) (4)
Best, Francis

From: Wholley, David (FNIH) [T]
Sent: Tue, 1 Aug 2017 18:04:04 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Subject: RE: [REDACTED] (b) (4) and PACT

Outstanding, Francis! I will send her what she needs.

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From: Collins, Francis (NIH/OD) [E]
Sent: Tuesday, August 01, 2017 1:38 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Lowy, Douglas (NIH/NCI) [E] [REDACTED] (b) (6); Doroshow, James (NIH/NCI) [E] [REDACTED] (b) (6); Tabak, Lawrence (NIH/OD) [E] [REDACTED] (b) (6); Wolinetz, Carrie (NIH/OD) [E] [REDACTED] (b) (6); Baker, Rebecca (NIH/OD) [E] [REDACTED] (b) (6)
Subject: [REDACTED] (b) (4) and PACT

Hi David,


(b) (4), (b) (5)

Francis

From: Wholley, David (FNIH) [T]
Sent: Thu, 13 Jul 2017 12:46:40 -0400
To: Collins, Francis (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - [REDACTED] (b) (4)
Importance: High

Francis, as promised, here is the summary background you requested:

(b) (4), (b) (5)



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From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, July 13, 2017 12:05 PM
To: Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6);
Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)
(b) (6) David/Stacey might be able to help with phone numbers that would get through.
The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Mon, 24 Jul 2017 18:21:49 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Monday, July 24, 2017 6:03 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - (b) (4)

OK. (b) (4), (b) (5)
(b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Monday, July 24, 2017 2:01 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - (b) (4)

Hi Francis— (b) (4), (b) (5)
I have followed up (b) (4), (b) (5)

(b) (4), (b) (5) Thanks, David

David Wholley
Director, Research Partnerships
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fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Sunday, July 23, 2017 7:43 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - (b) (4)

Hi David,

(b) (6) despite our pulling you into a couple of calls.

(b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Friday, July 14, 2017 8:50 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

David Wholley
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From: Collins, Francis (NIH/OD) [E]
Sent: Friday, July 14, 2017 6:39 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnihi.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Thursday, July 13, 2017 5:24 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnihi.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, July 13, 2017 5:08 PM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnihi.org> (b) (4)
Subject: Re: urgent phone calls to set up - (b) (4)

Great call

(b) (4), (b) (5)

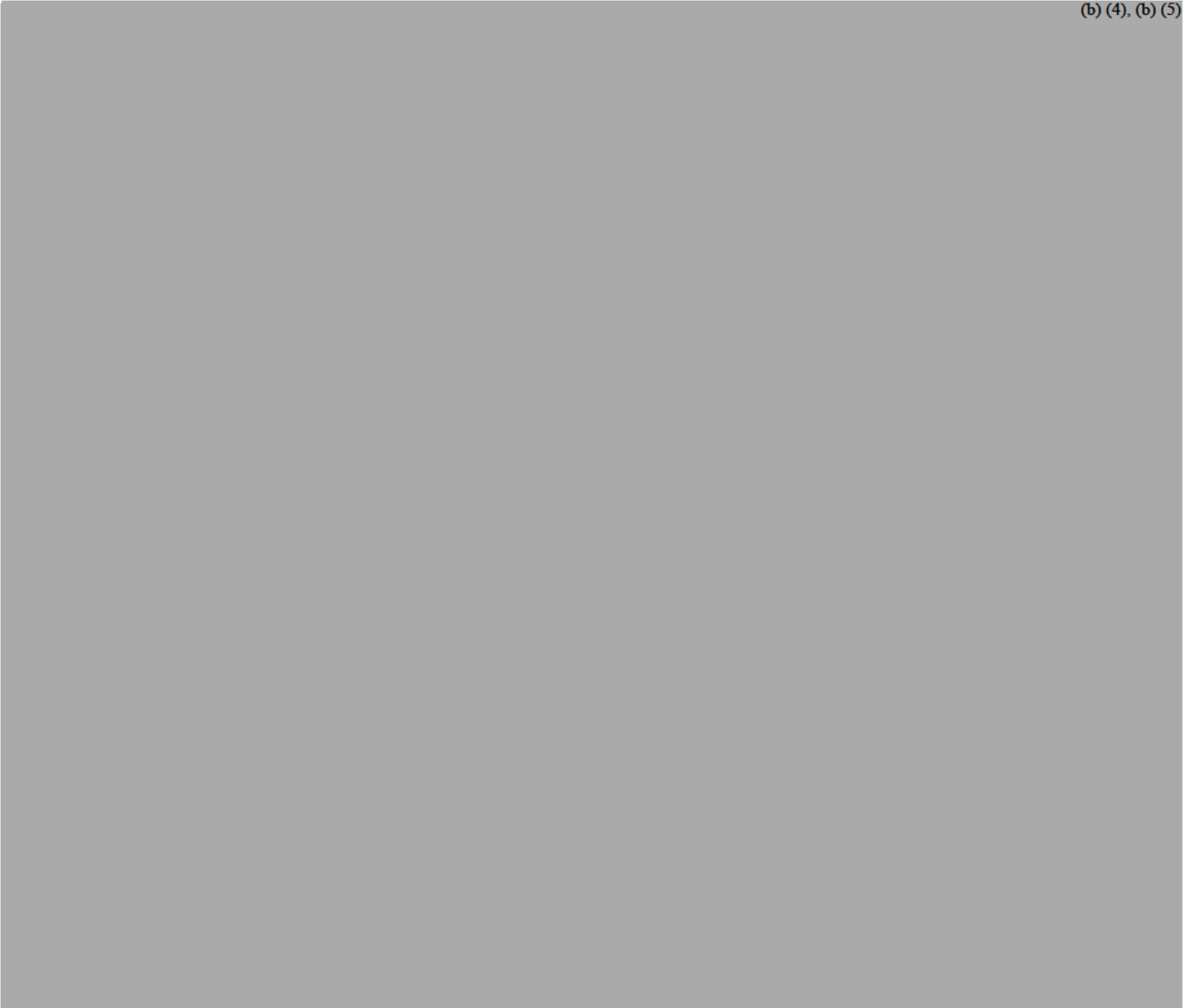
(b) (4), (b) (5)

Sent from my iPhone

On Jul 13, 2017, at 12:46 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

Francis, as promised, here is the summary background you requested:

(b) (4), (b) (5)



David Wholley
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From: Collins, Francis (NIH/OD) [E]

Sent: Thursday, July 13, 2017 12:05 PM

To: Wood, Gretchen (NIH/OD) [E] (b) (6)

Cc: Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Baker, Rebecca (NIH/OD) [E] (b) (6)

Wolinetz, Carrie (NIH/OD) [E] (b) (6) Adam, Stacey (FNIH) [T] <sadam@fnihi.org>

Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)

(b) (4), (b) (5) David/Stacey might be able to help with phone numbers that would get through.

The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Thu, 13 Jul 2017 12:41:27 -0400
To: Wood, Gretchen (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up

About to send an email with some assistant info--

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fnih.org

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From: Wood, Gretchen (NIH/OD) [E]
Sent: Thursday, July 13, 2017 12:34 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up

FC—

My contact for (b) (4), (b) (5) is on holiday and my contact for (b) (4), (b) (5) is no longer.

I have direct cells for both if you prefer to cold call. Otherwise I am happy to send them each a note.

(b) (4), (b) (5)

From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, July 13, 2017 12:05 PM
To: Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)
(b) (4), (b) (5) David/Stacey might be able to help with phone numbers that would get through.
The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Thu, 9 Nov 2017 00:29:01 +0000
To: Chin, Bill
Cc: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Subject: Re: Who Would Develop A Discarded Asset?

I think next step would be to [REDACTED]

(b) (4)

(b) (4)

Sent from my BlackBerry 10 smartphone.

From: Chin, Bill
Sent: Wednesday, November 8, 2017 7:21 PM
To: Wholley, David (FNIH) [T]
Cc: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Subject: Who Would Develop A Discarded Asset?

David, I just spoke to my former Lilly colleague, Rob Armstrong, who is currently CEO, Boston Pharmaceuticals [<http://www.bostonpharmaceuticals.com/whatwedo.php>]. His company essentially takes discarded assets, or repurposes same, and seeks to develop them. I asked him what models might be employed to perform this translational work. He suggested 3 approaches. [REDACTED]

(b) (4)

(b) (4)

(b) (4)

[REDACTED] Rob would entertain a call, if you wish. His email = rob@bostonpharmaceutical.com Let me know if I can answer any questions. Bill

PS Francis— [REDACTED]

(b) (4)

From: Wholley, David (FNIH) [T]
Sent: Tue, 3 Oct 2017 18:55:48 +0000
To: Collins, Francis (NIH/OD) [E]; Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Tabak, Lawrence (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Cc: Adam, Stacey (FNIH) [T]; Myles, Renate (NIH/OD) [E]
Subject: (b) (4) - update

Hi all: FYI Stacey Adam and I just got off a longish call with some of the decision-makers on PACT at (b) (4), (b) (5) to answer their questions about the revised design for PACT. It went well and we think (b) (4), (b) (5)
(b) (4), (b) (5)

David

David Wholley
Director, Research Partnerships
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(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Mon, 21 Aug 2017 22:57:32 +0000
To: Collins, Francis (NIH/OD) [E]; Sutherland, Margaret (NIH/NINDS) [E]; Koroshetz, Walter (NIH/NINDS) [E]
Cc: NIHDirectorMeetings; Canet-Aviles, Rosa (FNIH) [T]; Melencio, Cheryl (FNIH) [T]
Subject: Tanya Fischer, new AMP PD co-chair, will attend Friday's EC call

Sent from my BlackBerry 10 smartphone.

From: Wholley, David (FNIH) [T]
Sent: Mon, 4 Dec 2017 02:51:31 +0000
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Cc: Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]
Subject: Template for Opioids Partnership White Paper
Attachments: Opioids Partnership - White Paper Outline 30Nov2017.docx

Francis, all –

Our team put together the attached outline for the White Paper we are producing for Focus Area B (pain). I shared it with Bill Chin and he likes it, but had a couple of requests:

(b) (4), (b) (5)

(b) (4), (b) (7)

Thanks, David

We've moved! Please find our new address below.

David Wholley

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11400 Rockville Pike Suite 600 North Bethesda, MD 20852

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

From: Wholley, David (FNIH) [T]
Sent: Wed, 22 Nov 2017 21:18:33 +0000
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Stein, Jack (NIH/NIDA) [E]; Porter, Linda (NIH/NINDS) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]
Cc: Biarnes, Michael (FNIH) [T]; Menetski, Joseph (FNIH) [T]; Melencio, Cheryl (FNIH) [T]; McManus, Ayanna (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]
Subject: Updated Meeting Schedule
Attachments: Opioid meeting schedule 11-22-17.xlsx

All: for Friday's call. Please copy anyone I may have forgotten.
Happy Thanksgiving to all.
David

	OPIOID PARTNERSHIP MEETING SCHEDULES AS OF 11- 22-17						
Project	Co-Chairs	CoChair	Call 1A	Call 1B	Call 2	Call 3	Notes
Clinical Trials	Verburg (Pfizer) and Wright (NINDS)	Done	Done	Done	Dec. 1	N/A	Amir Tamiz (NINDS) added as second
Biomarkers	Mintun (Lilly) and Thomas (NIDA)	Done	Done	Done	Dec. 1	N/A	Yolanda Gallego (NIDCR) added as second
Data Sharing	Dunlop (Amgen) and Oshinsky (NIDA)	Done	Done	Nov. 28	Week of Dec. 4	N/A	
Asset Repurpose (SWAT)	Flores (Janssen) and Austin (NCATS)	N/A	Nov. 22	Nov 28,29	Dec 4,5		Flores, Austin, Verburg, Li (GSK), Dunlop, Christine Colvis (NCATS)
Co-Chair Only Meeting - Dec. 7							
FACE TO FACE: DECEMBER 12 and 13, North Bethesda Marriott							

From: Wholley, David (FNIH) [T]
Sent: Thu, 13 Jul 2017 15:13:07 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: urgent phone calls to set up - (b) (4)

Francis, as promised, here is the summary background you requested (b) (4), (b) (5) thanks to Stacey for her help in preparing):

(b) (4), (b) (5)



David

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From: Collins, Francis (NIH/OD) [E]

Sent: Thursday, July 13, 2017 12:05 PM

To: Wood, Gretchen (NIH/OD) [E] (b) (6)

Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6)

Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>

Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)

(b) (4), (b) (5) David/Stacey might be able to help with phone numbers that would get through.

The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

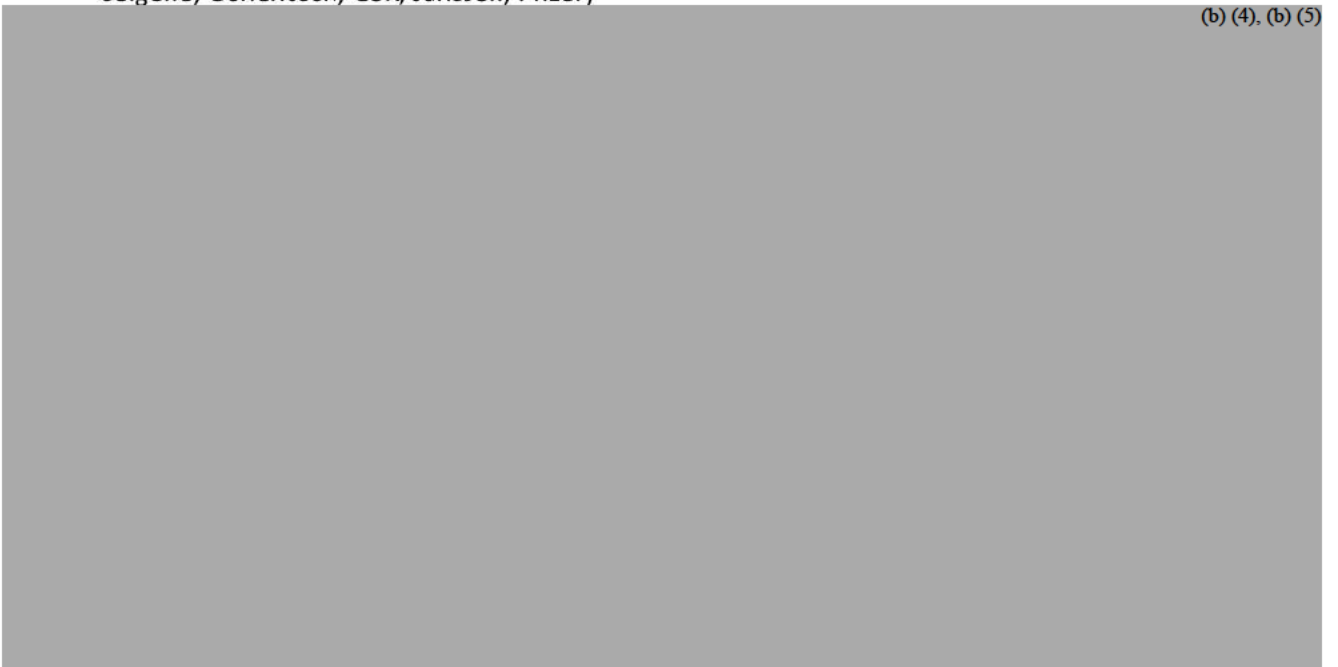
From: Wholley, David (FNIH) [T]
Sent: Mon, 2 Oct 2017 14:36:23 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: Where things stand on PACT

Francis,

Given we are "getting down to the wire" I thought I would give you a quick Monday morning update on where things stand with PACT:

- We are still at eight companies that have committed (AbbVie, BMS, Boehringer-Ingelheim, Celgene, Genentech, GSK, Janssen, Pfizer)

(b) (4), (b) (5)



- FNIH is providing support as needed to Renate on the rollout plan.

Please let me know if there is anything else you need at this point.

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From: Wholley, David (FNIH) [T]
Sent: Sat, 21 Oct 2017 01:25:10 +0000
To: Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Porter, Linda (NIH/NINDS) [E]; Burklow, John (NIH/OD) [E]
Subject: RE: URGENT: need feedback tonight on next steps for opioid PPP

(b) (5)

(b) (5) Francis.

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From: Collins, Francis (NIH/OD) [E]
Sent: Friday, October 20, 2017 6:06 PM
To: Baker, Rebecca (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Burklow, John (NIH/OD) [E] (b) (6); Wholley, David (FNIH) [T]
<dwholley@fnih.org>
Subject: URGENT: need feedback tonight on next steps for opioid PPP

Hi all,

Many thanks to Rebecca for putting together this draft of the solicitation we need to send out ASAP to the participating companies, following today's conference call.

I think this looks like a good list. Nora and Walter, are you OK with this? I'm also looping in David Wholley to seek his advice. Perhaps this time we should ask for two kinds of rating (b) (4), (b) (5)
(b) (4), (b) (5)

Though it would be great to know, (b) (4), (b) (5)
(b) (4), (b) (5)

FC

From: Baker, Rebecca (NIH/OD) [E]

Sent: Friday, October 20, 2017 3:39 PM

To: Collins, Francis (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E]

(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E]

(b) (6); Burklow, John (NIH/OD) [E] (b) (6)

Subject: Follow up: Invitation for first meeting of PPP to address the opioid crisis - Friday October 20, 11AM EDT

Good afternoon,

In follow up to today's discussion with industry partners, I am drafting a follow up note to capture interest in the possible PPP areas.

For your notes, please find below a new/revised list of possible areas of interest to ask of companies in response to today's discussion.

A similar set of requests was sent out in September in advance of the PhRMA BMAC meeting (September results attached), which we can refer to gently in our note.

New ideas coming out of today's discussion are marked in green.

With regard to planning for next week, it was my impression that this request would be to participate in the next stage of the planning process. If we are anticipating a White House event next week, this sorting exercise may not give us much new fodder for an announcement.

If we would like to be able to provide more information about what companies are planning to contribute, we might couple the interest poll with a request for information about in kind support.

This could be similar to what Bill shared in his weekend note (attached), which seems to be not limited to PhRMA groups.

In addition to the interest poll, is there any other information we should ask the companies for in the note we send tonight?

Thanks for your thoughts,

Rebecca

(b) (5)

From: Baker, Rebecca (NIH/OD) [E]
Sent: Thursday, October 19, 2017 11:58 PM
To: Collins, Francis (NIH/OD) [E] (b) (6); Tabak, Lawrence (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6)
Cc: Johnson, Ellie (NIH/NIDA) [E] (b) (6); NIHDirectorMeetings <NIHDirectorMeetings@mail.nih.gov>; Walker, Paula (NIH/NINDS) [E] (b) (6); McManus, Ayanna (NIH/OD) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6); Welch, Will (NIH/CIT) [C] (b) (6)
Subject: FW: Meeting Materials: Invitation for first meeting of PPP to address the opioid crisis - Friday October 20, 11AM EDT

NIH team,

Attached are a few additional material's for tomorrow's call:

1. Integrated slide presentation
2. Agenda
3. Roster of participating companies, current as of tonight
4. Original straw poll results of PhRMA companies who participated in September meetings

We have reserved space in Building 31, 6C room 7, adjacent to the CCRHB meetings so folks can step in and out.

Walter and Jack, dial-in information is below.

Thanks and see you tomorrow,

Rebecca

(b) (6)
Meeting number (access code): (b) (6)
Meeting password: (b) (6)

From: Baker, Rebecca (NIH/OD) [E]

Sent: Thursday, October 19, 2017 6:03 PM

To: Mark.Namchuk@alkermes.com; Markus.Haeberlein@alkermes.com; Armin.szegedi@allergan.com; jdunlop@amgen.com; gerard.marek@astellas.com; tolga.uz@astellas.com; pam.cyrus@bayer.com; james.baxter@boehringeringelheim.com; alfred.sandrock@biogen.com; Kate.dawson@biogen.com; rihargreaves@celgene.com; jfreeman@celgene.com; ktruit@dsi.com; andrew_satlin@eisai.com; laszlo.radvanyi@emdserono.com; cflores2@its.jnj.com; andyahn@lilly.com; mintun@avidrp.com; Min.x.li@gsk.com; Murray.w.steward@gsk.com; BKIN@Lundbeck.com; DTOL@Lundbeck.com; david.michelson@merck.com; allen.templeton@merck.com; Candace.saldarini@ODHsolutions.com; rmalamut@avanir.com; Kenneth.m.verburg@pfizer.com; Don.Kyle@pharma.com; Rita.BaliceGordon@Sanofi.com; Kenneth.koblan@sunovion.com; Gregg.redeker@takeda.com; Patricio.ODonnell@takeda.com; Ernest.kopecky@tevapharm.com; Eunan.maguire@adaptpharma.com; Fintan.keegan@adaptpharma.com; john.dunlop@amgen.com; Rafael.carbunaru@bsci.com; kbrose@chanzuckerberg.com; bdhammock@ucdavis.edu; schmidtwwk@sbcglobal.net; Christian.Heidbreder@indivior.com; anne.esposito@Indivior.com; Szale@lyndra.com; GFujii@molecularexpress.com; sdoberstein@nektar.com; pskolnick@opiant.com; rmalamut@avanir.com; owen.mcmanus@qstatebio.com; kbeebe@titanpharm.com; mlark@trevena.com; acrombie@trevena.com

Cc: Chin@phrma.org; Wolinetz, Carrie (NIH/OD) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Tabak, Lawrence (NIH/OD) [E] (b) (6); Collins, Francis (NIH/OD) [E] (b) (6); McManus, Ayanna (NIH/OD) [E] (b) (6); Wood, Gretchen (NIH/OD) [E] (b) (6); Johnson, Ellie (NIH/NIDA) [E] (b) (6); Walker, Paula (NIH/NINDS) [E] (b) (6); NIHDirectorMeetings <NIHDirectorMeetings@mail.nih.gov>; Fields, Ellen (FDA/CDER) (b) (6); Winchell, Celia J (FDA/CDER) (b) (6); Lin, Allison (FDA/CDER) (b) (6)

Subject: Meeting Materials: Invitation for first meeting of PPP to address the opioid crisis - Friday October 20, 11AM EDT

Good afternoon,

Please find attached materials for tomorrow's teleconference.

WebEx information can be found in the agenda, and is also pasted below.

Please feel free to reach out with any questions.

Thank you,

Rebecca

Join WebEx meeting

Meeting number (access code): (b) (6)

Meeting password (b) (6)

Join by phone

(b) (6) Call-in toll number (US/Canada)

Global call-in numbers

Can't join the meeting?

From: Collins, Francis (NIH/OD) [E]

Sent: Tuesday, October 17, 2017 6:50 PM

To: Eunan.maguire@adaptpharma.com; Fintan.keegan@adaptpharma.com; Mark.Namchuk@alkermes.com; Markus.Haeberlein <Markus.Haeberlein@alkermes.com>; Armin.Szegedi@allergan.com; john.dunlop@amgen.com; pam.cyrus@bayer.com; alfred.sandrock@biogen.com; Rafael.carbunaru@bsci.com; rihargreaves@celgene.com; jfreeman@celgene.com; kbrose@chanzuckerberg.com; ktruit@dsi.com; bdhammock@ucdavis.edu; andrew_satlin@eisai.com; andy.ahn@lilly.com; mintun@avidrp.com; schmidtwk@sbcglobal.net; laszlo.radvanyi@emdserono.com; "Min.x.li@gsk.com; Murray.w.steward@gsk.com; "; Christian.Heidbreder@indivior.com; cflores2@its.jnj.com; Steve Zale <Szale@lyndra.com>; allen.templeton@merck.com; david.michelson@merck.com; GFujii@molecularexpress.com; sdoberstein@nektar.com; pskolnick@opiant.com; "Candace.saldarini@ODHsolutions.com; rmalamut@avanir.com; Don.Kyle@pharma.com; Richard.Mannion@pharma.com; Kenneth.m.verburg@pfizer.com; owen.mcmanus@qstatebio.com; Rita.Balice-Gordon@sanofi.com; Kenneth.koblan@sunovion.com; gregg.redeker@takeda.com; Patricio.ODonnell@takeda.com; Ernest.Kopecky@tevapharm.com; kbeebe@titanpharm.com; "mlark@trevena.com; acrombie@trevena.com

Cc: Chin@phrma.org; Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Stein, Jack (NIH/NIDA) [E] (b) (6); Volkow, Nora (NIH/NIDA) [E] (b) (6); Koroshetz, Walter (NIH/NINDS) [E] (b) (6); Porter, Linda (NIH/NINDS) [E] (b) (6); Wholley, David (FNIH) [T] <dwholley@fnih.org>; Tabak, Lawrence (NIH/OD) [E] (b) (6)

Subject: Invitation for first meeting of PPP to address the opioid crisis - Friday October 20, 11AM

Dear Colleague,

Thank you for agreeing to participate in the development of a public-private partnership to address the national opioid crisis. As you know, our discussions to date have allowed us to focus on two areas for the partnership:

1. Develop new formulations and combinations of medications to treat opioid use disorders and prevent and reverse overdose
2. Develop new non-addictive pain therapies.

The next steps involve putting these focus areas into action which will entail convening experts from industry, academia, and the Foundation for the NIH. We will be asking you to commit to participating in a series of teleconferences (a couple of hours each) over the next several weeks and at least one in-person full-day meeting in November or December to establish consensus on a high-level plan. Given the magnitude of the crisis, and the strong interest of the current Administration and the Congress in finding solutions, we'd like to solidify a plan and identify any initial funding commitments by the end of this year, with a view to beginning work in early 2018.

In order to launch the planning effort, we are inviting you to participate in an inaugural conference call this **Friday, October 20, from 11:00 AM to 12:30 PM** Eastern U.S. time. We will outline our current thinking on potential research projects, describe the planning process we propose to follow, identify industry, NIH/academic chairpersons for these efforts, and seek your feedback.

Please find below the call-in and WebEx information; please RSVP to Rebecca Baker at

(b) (6)

We look forward to your joining us this Friday and to working with you on addressing this major public health challenge.

Regards,

Francis S. Collins, M.D., Ph.D.
Director, NIH

Stephen J. Ubl
President and Chief Executive Office, PhRMA

Join WebEx meeting

Meeting number (access code): (b) (6)

Meeting password: (b) (6)

Join by phone

(b) (6) Call-in toll number (US/Canada)

Global call-in numbers

Can't join the meeting?

If you are a host, [go here](#) to view host information.

From: Wholley, David (FNIH) [T]
Sent: Mon, 24 Jul 2017 14:01:06 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - (b) (4)

Hi Francis—

(b) (4), (b) (5)

(b) (4), (b) (5) Thanks, David

David Wholley
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From: Collins, Francis (NIH/OD) [E]
Sent: Sunday, July 23, 2017 7:43 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - (b) (4)

Hi David,

(b) (6)

despite our pulling you into a couple of calls.

(b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Friday, July 14, 2017 8:50 AM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH)

[T] <sadam@fnihi.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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From: Collins, Francis (NIH/OD) [E]
Sent: Friday, July 14, 2017 6:39 AM
To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E]
(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6) Adam, Stacey (FNIH)
[T] <sadam@fnihi.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Thursday, July 13, 2017 5:24 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E]
(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6) Adam, Stacey (FNIH)
[T] <sadam@fnihi.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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From: Collins, Francis (NIH/OD) [E]

Sent: Thursday, July 13, 2017 5:08 PM

To: Wholley, David (FNIH) [T] <dwholley@fnihi.org>

Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E]

(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnihi.org>

Subject: Re: urgent phone calls to set up - (b) (4)

Great call (b) (4), (b) (5)

(b) (4), (b) (5)

Sent from my iPhone

On Jul 13, 2017, at 12:46 PM, Wholley, David (FNIH) [T] <dwholley@fnihi.org> wrote:

Francis, as promised, here is the summary background you requested:

(b) (4), (b) (5)

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, July 13, 2017 12:05 PM
To: Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6)
Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)
(b) (4), (b) (5) David/Stacey might be able to help with phone numbers that would get through.
The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Sun, 23 Jul 2017 22:17:06 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: Re: urgent phone calls to set up [REDACTED] (b) (4)

Ball is in my court. [REDACTED] (b) (4), (b) (5)

[REDACTED] (b) (4), (b) (5)

Sent from my BlackBerry 10 smartphone.

From: Collins, Francis (NIH/OD) [E]
Sent: Sunday, July 23, 2017 7:42 PM
To: Wholley, David (FNIH) [T]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - [REDACTED] (b) (4)

Hi David,

[REDACTED] (b) (6)

despite our pulling you into a couple of calls.

[REDACTED] (b) (4), (b) (5)

FC

From: Wholley, David (FNIH) [T]
Sent: Friday, July 14, 2017 8:50 AM
To: Collins, Francis (NIH/OD) [E] [REDACTED] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] [REDACTED] (b) (6); Baker, Rebecca (NIH/OD) [E] [REDACTED] (b) (6); Wolinetz, Carrie (NIH/OD) [E] [REDACTED] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - [REDACTED] (b) (4)

[REDACTED] (b) (4), (b) (5)

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

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From: Collins, Francis (NIH/OD) [E]
Sent: Friday, July 14, 2017 6:39 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E]
(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH)
[T] <sadam@fnih.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Thursday, July 13, 2017 5:24 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E]
(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH)
[T] <sadam@fnih.org> (b) (4)
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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From: Collins, Francis (NIH/OD) [E]
Sent: Thursday, July 13, 2017 5:08 PM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E]
(b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH)
[T] <sadam@fnih.org> (b) (4)
Subject: Re: urgent phone calls to set up - (b) (4)

Great call

(b) (4), (b) (5)

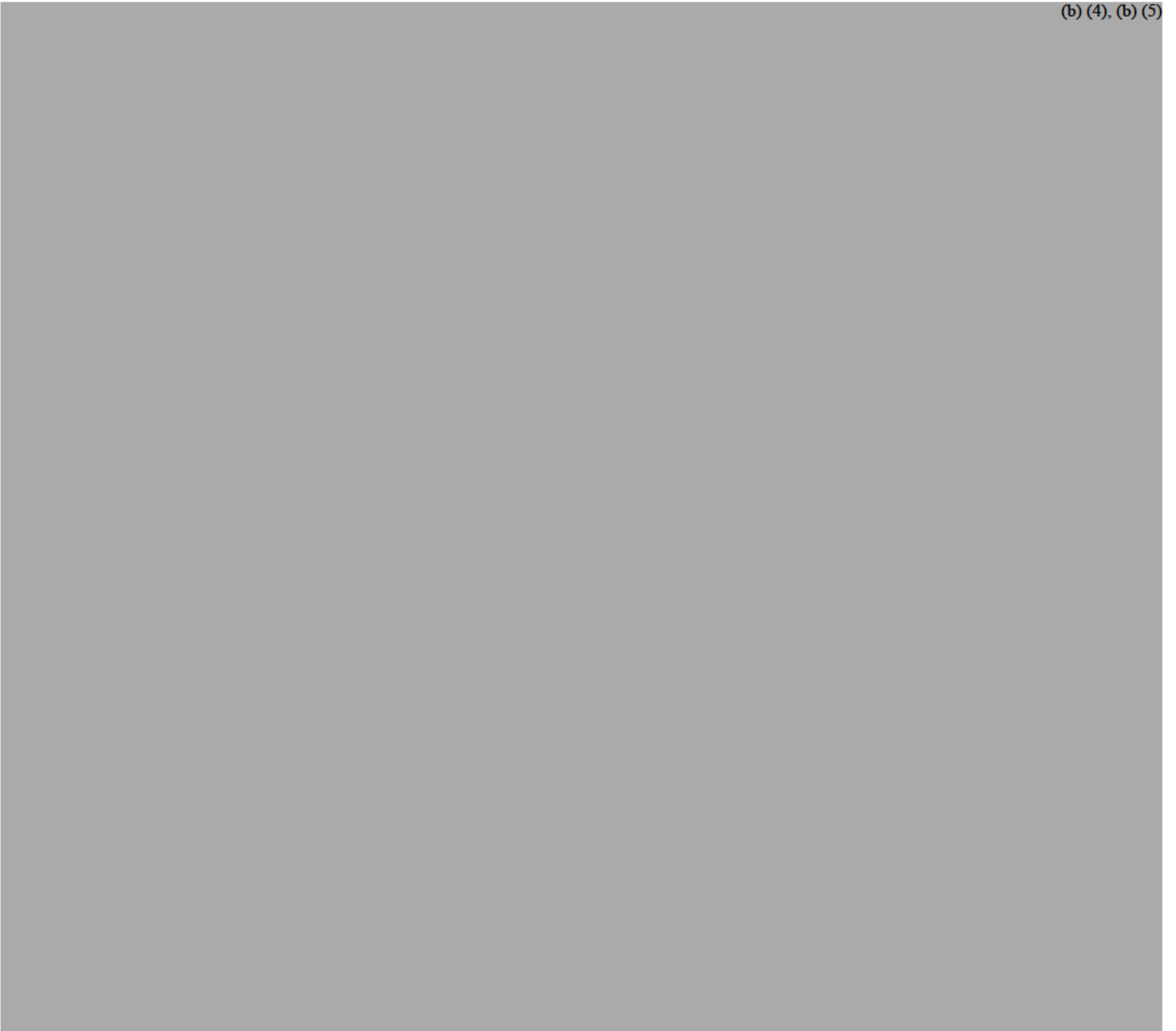
(b) (4), (b) (5)

Sent from my iPhone

On Jul 13, 2017, at 12:46 PM, Wholley, David (FNIH) [T] <dwholley@fnih.org> wrote:

Francis, as promised, here is the summary background you requested:

(b) (4), (b) (5)



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From: Collins, Francis (NIH/OD) [E]

Sent: Thursday, July 13, 2017 12:05 PM

To: Wood, Gretchen (NIH/OD) [E] (b) (6)

Cc: Wholley, David (FNIH) [T] <dwholley@fnihi.org>; Baker, Rebecca (NIH/OD) [E] (b) (6)

Wolinetz, Carrie (NIH/OD) [E] (b) (6) Adam, Stacey (FNIH) [T] <sadam@fnihi.org>

Subject: urgent phone calls to set up

If there's any way to do it, can you try to set up phone calls today (b) (4), (b) (5)

(b) (4), (b) (5) David/Stacey might be able to help with phone numbers that would get through.

The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Fri, 14 Jul 2017 08:50:16 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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Sent: Friday, July 14, 2017 6:39 AM
To: Wholley, David (FNIH) [T] <dwholley@fnih.org>
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up (b) (4)

(b) (4), (b) (5)

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Sent: Thursday, July 13, 2017 5:24 PM
To: Collins, Francis (NIH/OD) [E] (b) (6)
Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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Subject: Re: urgent phone calls to set up - (b) (4)

Great call

(b) (4), (b) (5)

(b) (4), (b) (5)

Sent from my iPhone

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Sent: Thursday, July 13, 2017 12:05 PM
To: Wood, Gretchen (NIH/OD) [E] (b) (6)
Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6);
Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: urgent phone calls to set up

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The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Thu, 13 Jul 2017 17:24:24 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - [REDACTED] (b) (4)

[REDACTED] (b) (4), (b) (5)

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Subject: Re: urgent phone calls to set up [REDACTED] (b) (4)

Great call [REDACTED] (b) (4), (b) (5)

[REDACTED] (b) (4), (b) (5)

Sent from my iPhone

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Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnihi.org>
Subject: urgent phone calls to set up

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The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Thu, 13 Jul 2017 17:21:04 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Wood, Gretchen (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: RE: urgent phone calls to set up - (b) (4)

(b) (4), (b) (5)

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Cc: Wood, Gretchen (NIH/OD) [E] (b) (6); Baker, Rebecca (NIH/OD) [E] (b) (6); Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: Re: urgent phone calls to set up (b) (4)

Great call

(b) (4), (b) (5)

(b) (4), (b) (5)

Sent from my iPhone

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Sent: Thursday, July 13, 2017 12:05 PM
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Cc: Wholley, David (FNIH) [T] <dwholley@fnih.org>; Baker, Rebecca (NIH/OD) [E] (b) (6)
Wolinetz, Carrie (NIH/OD) [E] (b) (6); Adam, Stacey (FNIH) [T] <sadam@fnih.org>
Subject: urgent phone calls to set up

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(b) (4), (b) (5) David/Stacey might be able to help with phone numbers that would get through.
The topic is the Partnership for Accelerating Cancer Therapies (PACT).

FC

From: Wholley, David (FNIH) [T]
Sent: Wed, 22 Feb 2017 20:42:41 -0500
To: Collins, Francis (NIH/OD) [E]
Cc: Gadbois, Ellen (NIH/OD) [E]; Canet-Aviles, Rosa (FNIH) [T]
Subject: AMP PD update

Hi Francis, just so you know (b) (4) have re-confirmed their interest in funding AMP PD
(b) (4) so no need to bring this up in front of (b) (4) We have four
confirmed funders and are just waiting (b) (4).
David

From: Wholley, David (FNIH) [T]
Sent: Fri, 27 Jan 2017 15:01:47 -0500
To: Melencio, Cheryl (FNIH) [T]; Buckholtz, Neil (NIH/NIA) [C]; Canet-Aviles, Rosa (FNIH) [T]; Carter, Robert (NIH/NIAMS) [E]; Collins, Francis (NIH/OD) [E]; Cuss, Francis; Decker, Mike; Dolsten, Mikael; Gadbois, Ellen (NIH/OD) [E]; Hodes, Richard (NIH/NIA) [E]; Hodge, Martin; Hoffmann, Steve (FNIH) [T]; Katz, Stephen I. (NIH/NIAMS) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Lea, Allison (NIH/OD) [E]; Lifton, Richard; Lundberg, Jan; Paltoo, Dina (NIH/OD) [E]; Rodgers, Griffin (NIH/NIDDK) [E]; Ryan, Laurie (NIH/NIA) [E]; Serrate-Sztejn, Susana (NIH/NIAMS) [E]; Smith, Philip (NIH/NIDDK) [E]; Spear, Nicole (FNIH) [T]; Sutherland, Margaret (NIH/NINDS) [E]; Tabak, Lawrence (NIH/OD) [E]; Terry, Sharon MA
Cc: Boskent, Celeste (NIH/OD) [E]; Bronson, Charlette (NIH/NIA) [E]; Burrus-Shaw, Cyndi (NIH/OD) [E]; Clark, Katie; Craver, Stephanie (NIH/NIAMS) [E]; Doswell, Greta (NIH/OD) [E]; Edmonds, Pamela; Yuliya Ilchuk; McManus, Ayanna (NIH/OD) [E]; Meltzer, Sherry (NIH/NIAMS) [E]; Morgan, Emily (FNIH) [T]; Tanya Murza; NIH Director Meetings; Poniente, Josefina; Poole, Charlene (NIH/NIDDK) [C]; Protasiewicz, Ann; Schulke, Hilda (NIH/NIDA) [E]; Sheehan, Joan (NIH/NIA) [E]; Simon, Dina (NIH/OD) [C]; Walker, Paula (NIH/NINDS) [E]; Wood, Gretchen (NIH/OD) [E]; Zander, Debra
Subject: AMP RA/SLE Program Milestone

Dear AMP Executive Committee Members,

As you may recall from our recent Executive Committee calls, the AMP RA/SLE Steering Committee (SC) had decided in September to delay a vote on the go/no go milestone for the program for several months in order to allow more detailed analysis of the data generated from analysis of human samples collected as part of Phase I of the program.

I am pleased to report to you that yesterday the SC voted unanimously to approve the continuation of the program. The “go” vote included representatives from all 6 industry partners, 2 patient advocacy organizations, NIAMS and NIAID. With strong SC guidance from Bob Carter (NIAMS) and Marty Hodge (Pfizer), and strong cooperation from the leadership of the investigative team under Michael Brenner (Brigham and Women’s Hospital), the process to reach this decision has renewed the team’s enthusiasm about our ability to identify and validate promising biological targets in rheumatoid arthritis and lupus and catalyzed additional collaborative interactions among the partners. Of note, the AMP team’s ability to generate expression profiles on thousands of single cells collected from the tissues of donors across the US and the UK is itself unprecedented and promises a paradigm shift in the deconstruction of these diseases.

As we’d previously discussed with you, the delay in adjudicating the RA/SLE milestone originally stemmed from the desire of the industry partners to have direct access to Phase 1 data and the ability to directly QC and verify the integrity and reproducibility of these data for likely success in Phase 2 analyses. To enhance the assessment of the milestone criteria and insure its feasibility, the SC enabled direct access to general and genomic, sequence-level data (both RNAseq and CYTOF data) for all of the AMP partners (with appropriate patient privacy safeguards), guaranteed interim funding to support NIH grants to investigators during the

evaluation period, and sponsored instructional webinars for the industry scientists with leading experts in RNASeq and CyTOF to better understand and prepare for the data QC and analytics to be performed. This helped greatly in establishing the credibility of the decision process and promoting comfort with the results.

The RA/SLE program will now move forward with their annual face-to-face meeting between the SC and investigator team leads in Houston on February 15th-17th, with a focus on planning for Phase 2 of the project. You can expect to hear more on the results of this on our next AMP EC call on February 24.

Of note, the key midterm go/no-go milestones for all of the AMP research programs have now been achieved.

Regards,

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health

From: Wholley, David (FNIH) [T]
Sent: Tue, 7 Nov 2017 23:21:32 +0000
To: Flores, Christopher [CONUS]
Cc: Collins, Francis (NIH/OD) [E]; Chin, Bill (Chin@phrma.org); Baker, Rebecca (NIH/OD) [E]; Biarnes, Michael (FNIH) [T]
Subject: Asset Repurposing/Development for Pain

Dear Chris –

Thank you again for taking the time this afternoon to share with me your concerns about the pain medication development portion of the opioid partnership. As promised, I have discussed this further with both Francis Collins and Bill Chin, and we agree that finding a way to incorporate the offer of specific assets—chemical, technology, data or otherwise—from companies into the partnership is distinct from “data sharing” as described in the plan and represents a near-term opportunity we need to figure out how to take advantage of. Rather than run this as part of the larger workstreams, we are wondering if perhaps a better approach might not be to get together a smaller group of companies with assets to offer in the pain space for a focused discussion to figure out how best to move this forward on a fast track. We’d involve folks from NINDS and NCATS on the NIH side, and thought we could start with you and perhaps Ken Verbarg among the company representatives. Would you be amenable to that approach, and if so are there a few other company folks you think we should invite? Please let me know.

Thanks,
David

We’ve moved! Please find our new address below.

David Wholley

Director, Research Partnerships

Foundation for the National Institutes of Health

(301) 594-6343

fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

*Learn more about the FNIH in our **2016 Annual Report**: fnih.org/AnnualReport.*

From: Wholley, David (FNIH) [T]
Sent: Mon, 13 Nov 2017 02:51:12 +0000
To: Flores, Christopher [CONUS]; Austin, Christopher (NIH/NCATS) [E]; Kenneth.m.verburg@pfizer.com; min.x.li@gsk.com; john.dunlop@amgen.com; Colvis, Christine (NIH/NCATS) [E]; Chin, Bill (Chin@phrma.org); Koroshetz, Walter (NIH/NINDS) [E]
Cc: Volkow, Nora (NIH/NIDA) [E]; Stein, Jack (NIH/NIDA) [E]; Wright, Clinton (NIH/NINDS) [E]; Mark Mintun; Thomas, David (NIH/NIDA) [E]; Oshinsky, Michael (NIH/NINDS) [E]; Biarnes, Michael (FNIH) [T]; Melencio, Cheryl (FNIH) [T]; Collins, Francis (NIH/OD) [E]; Baker, Rebecca (NIH/OD) [E]; Porter, Linda (NIH/NINDS) [E]
Subject: Asset Repurposing Group for Opioids Partnership

Dear colleagues:

As you know we have been pushing forward on specific plans for an opioids partnership to accelerate new treatments for OUD, overdose, and pain. In the pain focus area, FNIH has already formed three Working Groups—in data sharing, biomarkers, and clinical trials networks and design—with a broad array of stakeholders, and NIDA is engaging a number of companies to explore new formulations and combinations of therapies to address overdose and OUD. It has come to our attention, however, that there may be opportunities to share specific chemical assets, technologies and related datasets that are not adequately covered by the existing working group arrangements, particularly in pain. After conferring with the leadership of the partnership we've decided to convene a focused team to consider these opportunities and how best to address them. Chris Flores of Johnson & Johnson and Chris Austin of NCATS will lead this discussion.

I am asking the addressees on this note to form the core of this group and also ask if we can set aside 60 minutes or so for an initial call sometime in the next week or two to discuss what assets may be available and how best to approach a plan for deploying them in support of the partnership. To provide a broader view (and ensure continuity with other efforts) I am also inviting Nora Volkow and Jack Stein from NIDA and the co-chairs of the three pain Working Groups to join the conversation if they can. Can you please respond to Cheryl Melencio on our staff, who will be sending out a poll shortly for this call?

I look forward to our discussion.

Regards,
David Wholley

We've moved! Please find our new address below.

David Wholley

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From: Wholley, David (FNIH) [T]
Sent: Tue, 12 Dec 2017 02:33:18 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: Automatic reply: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

I will be helping to manage a scientific meeting all day on December 12 and 13 and will have limited ability to respond to other matters. Best way to reach me if urgent is via email.

From: Wholley, David (FNIH) [T]
Sent: Mon, 16 Oct 2017 14:14:34 +0000
To: Collins, Francis (NIH/OD) [E]
Subject: Automatic reply: can you call in at noon?

I am out of the office on annual leave until Tuesday, September 5. For urgent matters please call or email Cheryl Melencio (cmelencio@fnih.org or (b) (6))

From: Wholley, David (FNIH) [T]
Sent: Fri, 3 Nov 2017 14:26:55 +0000
To: Collins, Francis (NIH/OD) [E];Koroshetz, Walter (NIH/NINDS) [E];Tabak, Lawrence (NIH/OD) [E];Volkow, Nora (NIH/NIDA) [E]
Cc: Porter, Linda (NIH/NINDS) [E];Baker, Rebecca (NIH/OD) [E];Wolinetz, Carrie (NIH/OD) [E];Stein, Jack (NIH/NIDA) [E];Biarnes, Michael (FNIH) [T];Menetski, Joseph (FNIH) [T];Melencio, Cheryl (FNIH) [T];McManus, Ayanna (NIH/OD) [E]
Subject: Availability week of December 11 for Opioids face to face meeting

Dear All—

Since our meeting yesterday our FNIH Events group has identified several possible venues for a 2-day face to face meeting on opioids. I recall from yesterday that several of you mentioned you had some conflicts or previous engagements that week. In the interest of nailing down a venue (which get filled fast this time of year) and the meeting dates, can you please advise us immediately as to your preferred 2-day slot that week? I would imagine that given the emphasis on pain the schedules for Francis, Walter, and Linda would be particularly critical. A reply today would be greatly appreciated.

Thanks,
David

We've moved! Please find our new address below.

David Wholley

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From: Wholley, David (FNIH) [T]
Sent: Thu, 5 Oct 2017 23:06:42 +0000
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Hodes, Richard (NIH/NIA) [E]
Subject: Changes at Lilly--Lundberg retiring

In case you had not heard:

<https://www.reuters.com/article/lilly-cfo/lilly-names-new-cfo-replaces-head-of-rd-in-management-shakeup-idUSL2N1MAOSE>

From: Wholley, David (FNIH) [T]
Sent: Mon, 9 Jan 2017 18:41:00 -0500
To: Collins, Francis (NIH/OD) [E]
Subject: Do you have a moment to chat?

Francis, I have an issue I need to discuss with you by phone—email not appropriate. Would you have any time to speak for maybe 5 minutes in the next few days? Thanks David

From: Wholley, David (FNIH) [T]
Sent: Wed, 3 May 2017 15:28:05 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Lowy, Douglas (NIH/NCI) [E]; Doroshow, James (NIH/NCI) [E]; Baker, Rebecca (NIH/OD) [E]; Adam, Stacey (FNIH) [T]
Subject: Draft note to Celgene
Attachments: PACT Partner Briefing Deck 021017vF4.pdf, PACT_Whitepaper_022817.pdf, PACT Executive Summary 5-3-17.pdf

Dear Mark:

It was a pleasure to meet you at the Milken LA meeting, and I'm glad we got a chance to talk about the Partnership for Accelerating Cancer Therapies (PACT), which we have been developing with multiple pharmaceutical companies and FDA over the last eight months or so. As we discussed, PACT is focused on the critical issue of developing better biomarkers for selecting and testing cancer immunotherapies and relevant combinations. Following up your request for more information, I have attached a text executive summary and a slide deck overviewing the partnership, as well as the full text of the white paper that contains the initial research plan for those who may need more detail.

I'm very glad to hear you may be interested in having Celgene consider joining PACT. We are looking to determine a final set of committed partners by the end of June or so, with the plan to reconvene them thereafter along with our FDA colleagues to work out the final research plan in more detail, so there is still ample room for input here from Celgene should you decide to participate. If you or any of your colleagues want to follow up on the financial implications of participation—or indeed any aspect of PACT—I would ask that you contact David Wholley (copied) at the Foundation for the NIH, who have been overseeing the project development and fundraising aspects of this.

Sincerely,
Francis

Partnership for Accelerating Cancer Therapies (PACT)

Slides for Partner Briefings
February 2017



NIH - 002473

The Foundation for the National Institutes of Health (FNIH) will be the program managers for PACT

The FNIH was established by Congress in 1990 as a not-for-profit 501(c)(3) charitable organization



The Foundation began its work in **1996** to facilitate groundbreaking research at the NIH and worldwide



By creating effective alliances to advance biomedical research



501(c)(3)

Non-governmental
not-for-profit & independent
Board of Directors

More than **550**
projects supported

120+

active research partnerships,
scientific education/training,
conferences/events and
capital programs

93%

of funds directly
support programs



In 2016, Charity Navigator
gave FNIH a 4 star perfect
score rating. The FNIH ranks
in the top 1% of all
organizations ranked

13 years

of outstanding
Charity Navigator ratings

Select partnerships at the FNIH

- | | |
|--|---------------|
| • Accelerating Medicines Partnership
NIH (OD), NIA, NIAMS, NIDDK, 10 companies, 9 not-for-profit organizations | \$230 million |
| • Grand Challenges in Global Health (GCGH)
Bill & Melinda Gates Foundation | \$201 million |
| • LungMAP: Master Lung Protocol Trial
NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date | \$163 million |
| • Alzheimer's Disease Neuroimaging Initiative (ADNI)
NIA, NIBIB, 25+ companies, 3 not-for-profit organizations | \$148 million |
| • Vector-Based Control of Transmission (VCTR)
VRC/NIAID, Bill & Melinda Gates Foundation | \$78 million |
| • The Biomarkers Consortium
<i>FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations</i> | \$72 million |
| • Comprehensive T Cell Vaccine Immune Monitoring Consortium (CT-VIMC)
Bill & Melinda Gates Foundation, NIAID | \$50 million |
| • MAL-ED: The Interactions of Malnutrition and Enteric Infections,
Effect on Childhood Development
Bill & Melinda Gates Foundation, Fogarty Institute Center (NIH) | \$46 million |

TOTAL: \$984 million

NIH - 002475

The pursuit of IO and combination therapies faces many challenges

Companies are pursuing hundreds of existing trials, yet:

- + Large number of potential combinations to be tested
 - + Lack of biomarkers to predict and understand patient outcomes
 - + Lack of robust, standardized assays
 - + Lack of reproducibility of data across trials
- = Need to fill knowledge gaps and efficiently use research resources*

Solution: A systematic effort to develop and share biomarker and related clinical data to support clinical testing of combination therapies – PACT

PACT was developed in response to these challenges as one of the Cancer Moonshot Initiative programs



CANCER MOONSHOT



“ I plan to do two things: increase resources—both private and public—to fight cancer, and break down silos and bring all the cancer fighters together—to work together, share information, and end cancer as we know it. ”

Vice President Joseph Biden
February 2016



NIH - 002477

The design of PACT represents consensus from industry, government, and academic experts in the field

PACT is a public-private partnership being developed as part of the Cancer Moonshot effort. FNIH has led an initial research design effort over the past 6 months involving 42 scientists from NCI, FDA, and 14 companies:

- AbbVie
- Amgen
- AstraZeneca
- Bayer
- Boehringer-Ingelheim
- BMS
- EMD Serono
- Genentech
- GSK
- Lilly
- Merck
- Novartis
- Pfizer
- Takeda

- Additional support provided by PhRMA

42 scientists contributed to PACT Design Phase whitepaper

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Two PACT program areas emerged from the Design Phase; Program Area 1 will focus on biomarker development and testing and infrastructure creation...

Program Area 1: Facilitate robust, systematic, uniformly conducted clinical testing of known and exploratory biomarkers that enable better understanding of response and resistance to IO combinations and guide treatment strategies

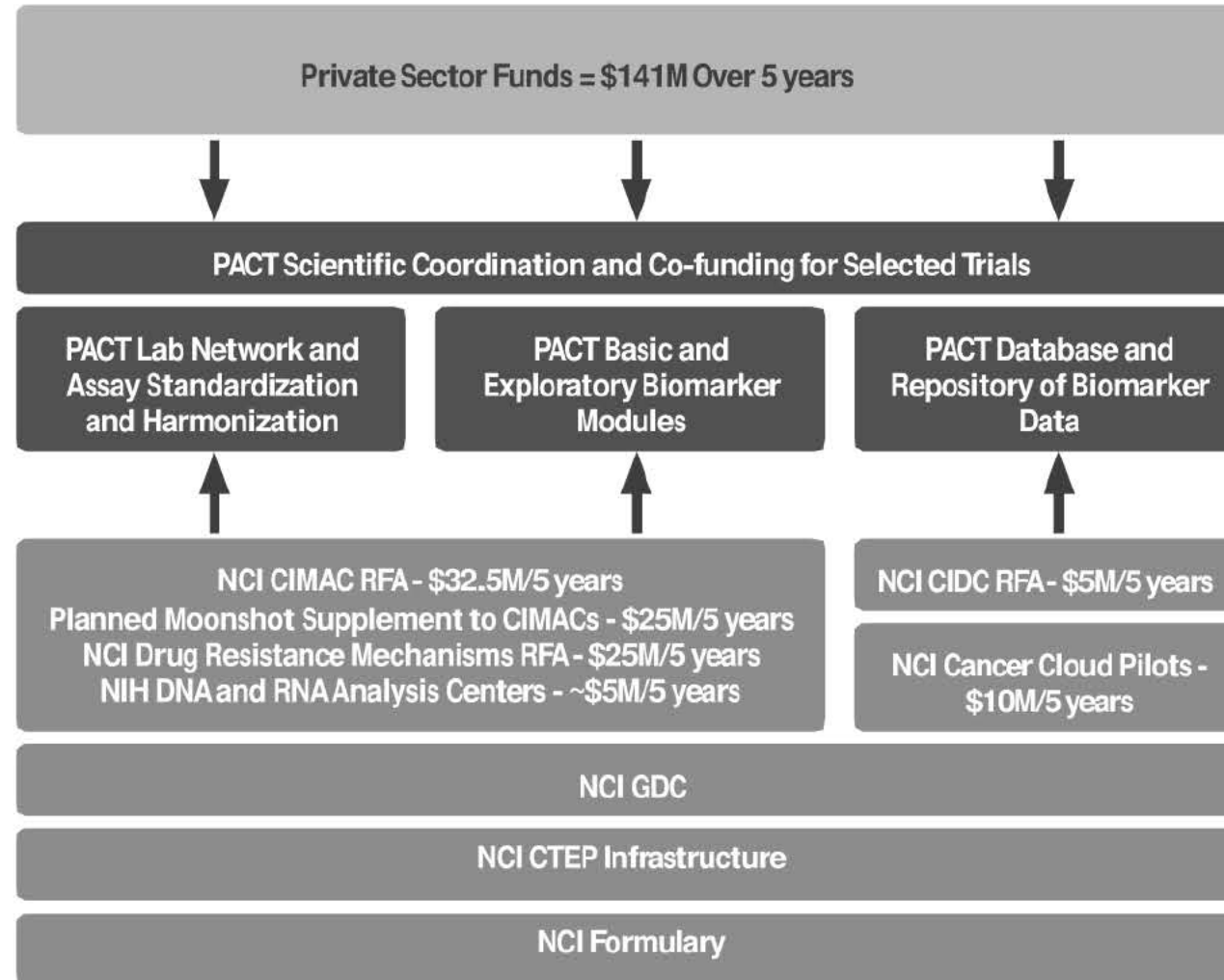
- Establish a **network of 3-5 core laboratories** to conduct, standardize, and validate biomarker assays
- Fund the **development of new exploratory biomarkers and assays** of high relevance to and impact on the field
- **Incorporate biomarker modules into trials** prioritized by PACT and coordinate their adoption broadly across the oncology research community
- Create a **comprehensive database** that integrates biomarker module and clinical data to enable pre-competitive correlative biomarker analyses

...while Program Area 2 will focus on strategic assessment of and outreach to the IO field, as well as coordination and co-funding of selected clinical trials

Program Area 2: Provide scientific coordination for the identification of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners.

- Create and maintain a “**landscape analysis**” of combination therapy trials and biomarkers across the IO space, enabling categorization of prospective new trials based on relevance
- Select and **co-fund high relevance combination trials** not already being performed by other entities, leveraging existing trial networks
- **Facilitate information sharing** by all stakeholders to better coordinate clinical/translational oncology programs, **align investigative approaches**, and enable the **most relevant trials to be conducted**
- Includes active outreach to other IO research efforts on an ongoing basis

PACT will build on current and planned NCI investments: recent RFAs and existing infrastructure provide a “shovel ready” foundation for PACT

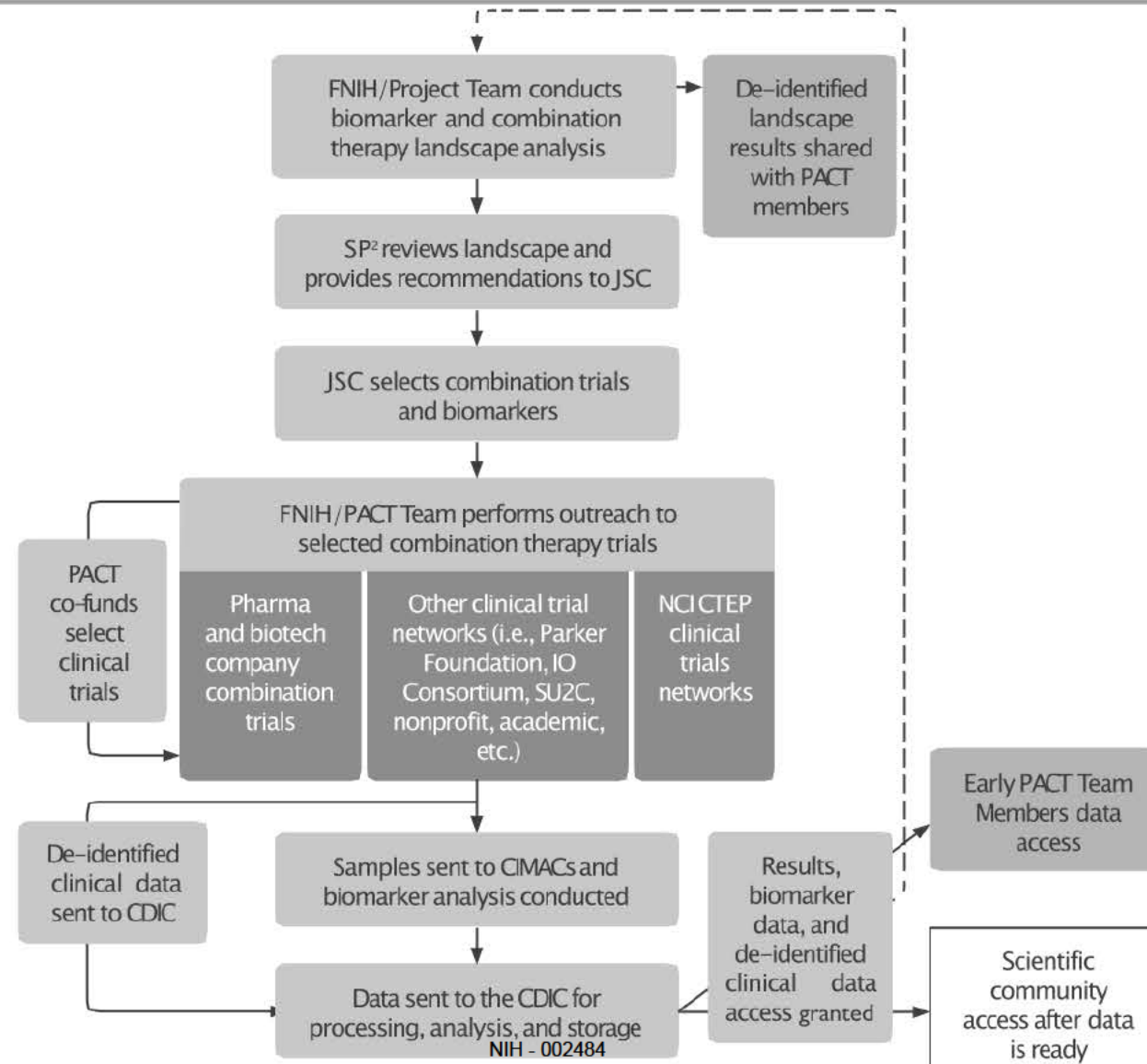


PACT total investment = \$251M over 5 years
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Three PACT Governance bodies will provide joint oversight – but with streamlined review procedures and policies



PACT offers a flexible, but efficient mechanism to develop novel markers and use them to select and test the most appropriate combination therapies

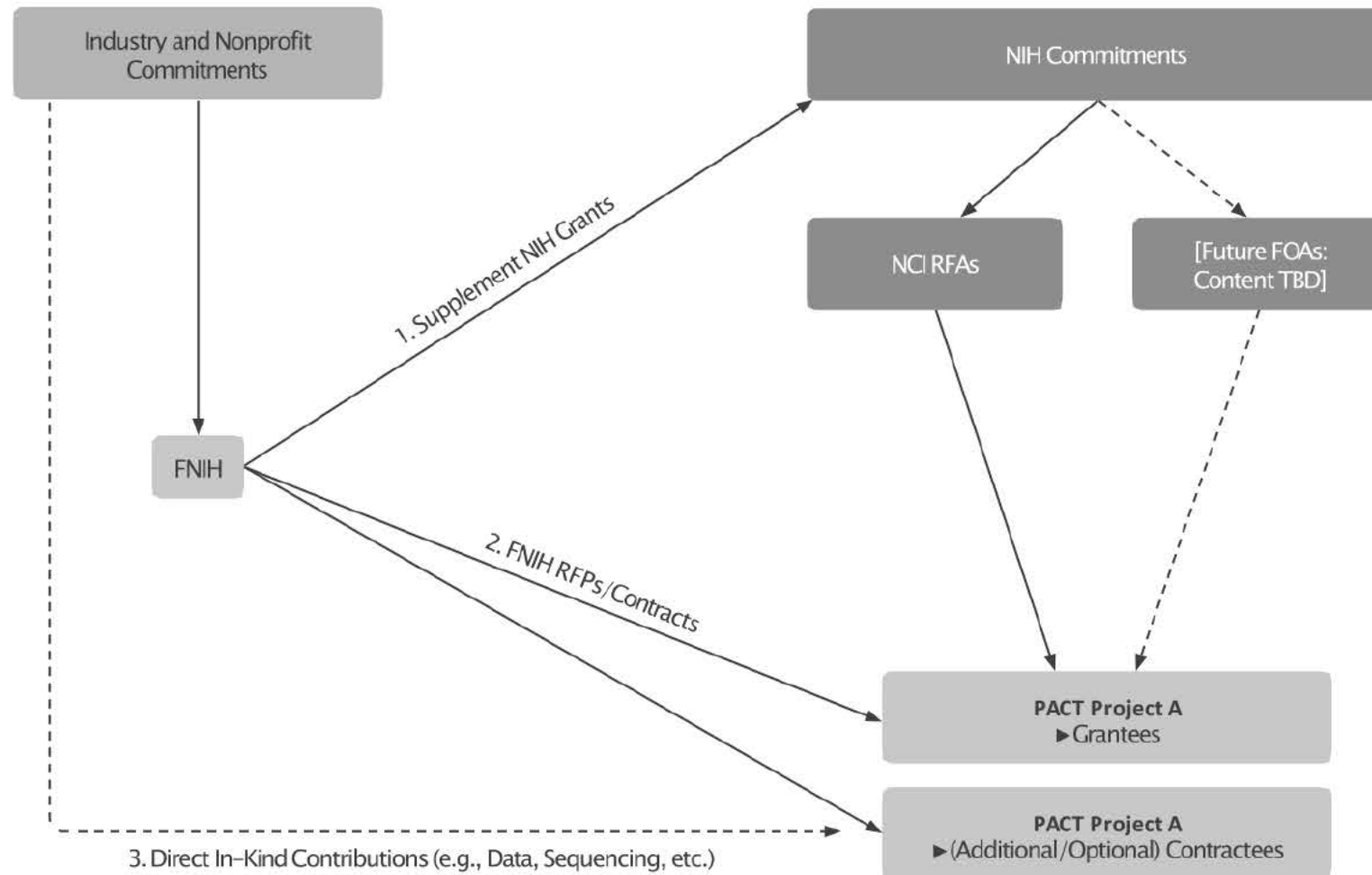


PACT will require total funding of ~\$251M over 5 years, with an investment of ~\$141M/5 years needed from the private sector

Consolidated Itemized PACT Budget		
All Costs Reflect Total Over 5 Years		
Project Plan Section	Budget Item/ Project Goal	Total Project Cost
Project 1.1.1 & 1.2	Create core laboratory network to conduct biomarker assays	(b) (4)
Project 1.3	Create database to bank IO biomarker data from clinical trial	
Project 1.4	Standardize and harmonize biomarker assays for IO therapy	
Project 1.1.2	Development of new IO biomarkers	
Project 1.1.2 & 1.4	Expansion biorepository capabilities for sample storage	
Program Area 1		
Project 2.1	Conduct bi-annual landscape analysis to determine priority biomarkers and combination therapies	
	Compensate SP ² members for trial and biomarker landscape review	
Project 2.2	PACT co-funding for high priority combination clinical trials	
Project 2.3	Outreach and coordination with other IO efforts	
Program Area 2		
FNIH Program Management Costs		
PACT Initiative Total		\$251M
Program Area 1 –“Buy-up” Option		
•Supplement to defray costs of tissue collection at clinical sites		
Program Area 2 – “Buy-up” Options		
•Additional co-funded clinical trials		

NIH

Private sector funds for can be deployed flexibly through FNIH to PACT in a variety of ways, as required by specific project needs



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The collaborative nature of PACT offers distinct—and considerable—value for its stakeholders and the oncology research community at large

- ☑ Core laboratories and database provide access to:
 - Standardized immune biomarkers modules, enabling a systematic approach across trials
 - Standardized, harmonized assay platforms, procedures, and best practices
 - Biomarker analyses to accelerate hypothesis testing
 - Clinical trial and biomarker landscape analyses
- ☑ Opportunities to initiate high relevance trials with PACT co-funding
- ☑ Data and insights to support regulatory decision-making
- ☑ More systematic approach to IO + combinations across the field
- ☑ Mechanism to share insights and resources with other Moonshot and IO collaborations

Private sector funders will have an direct voting role in further defining the PACT research plan and in PACT governing committees

The proposed PACT program also has synergies with several areas of recommendation from the Cancer Moonshot Blue Ribbon Panel

★ Potential PACT synergies

- Network for direct patient engagement
- Cancer immunotherapy translational trials network ★
- Therapeutic target identification to overcome drug resistance ★
- A national cancer data ecosystem for sharing and analysis ★
- Fusion oncoproteins in pediatric cancer
- Symptom management research
- Prevention and early detection: implementation of evidence-based approaches
- Retrospective analysis of biospecimens from patients treated with standard of care ★
- Generation of human tumor atlases ★
- Development of new enabling cancer technologies

Assuming timely success at funding PACT, we are aiming for an operational launch of the initiative in 3Q of this year

Next steps:

- ☐ Finalize PACT budget and white paper, distribute for review (February, 2017)
- ☐ Outreach to potential collaborators (patient organizations, non-profits, other companies, professional and standards organizations, etc.) (February-March, 2017)
- ☐ Partners identified and funds pledged via FNIH (March-June, 2017)
- ☐ FNIH will convene an in-person meeting with committed partners to develop detailed research plans for each project, including detailed budgets, timelines and milestones (3Q, 2017)
- ☐ Desired launch date of PACT (3Q, 2017)

NIH - 002490

Biomarkers to be Included in PACT

BASIC ASSAYS

(To be run on all patients in each trial)

- Peripheral Samples: Flow cytometry and CyTOF – 3 panels - T and B cell
- Tumor: immunohistochemistry
- Peripheral Samples: ELISA
- Whole exome sequencing (150X coverage)
- RNA-seq (150 million reads/sample)
- cfDNA (using DNA-seq)

EXPLORATORY ASSAYS

(Examples)

- Expanded flow cytometry (innate immune cell panels)
- CNVs
- SNPs
- Single cell/nuclei RNA-seq
- CTC
- T and B cell deep receptor sequencing
- cfRNA
- Microbes
- Exosomes
- Microvesicles
- Expanded immunohistochemistry
- Immunofluorescence
- Others TBD

Partnership for Accelerating Cancer Therapies (PACT)

FINAL DESIGN WHITEPAPER - FEBRUARY 2017



National Institutes
of Health



Foundation for the
National Institutes of Health

PACT Design Phase Sponsors

AbbVie, Inc.

Amgen, Inc.

AstraZeneca

Bayer AG

Boehringer-Ingelheim GmbH

Bristol-Myers Squibb

EMD Serono, Inc.

Genentech, Inc.

GlaxoSmithKline

Eli Lilly

Merck Sharp & Dohme Corp.

Novartis Pharmaceuticals

Pfizer, Inc.

Pharmaceutical Research and Manufacturers of America

Takeda Pharmaceutical Company Ltd

National Institutes of Health/National Cancer Institute

U.S. Food and Drug Administration

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Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$251 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, unifying clinical biomarker investigation, filling knowledge gaps, and integrating information from multiple sources, through two programs:

Program 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing a set of basic biomarker modules for uniform clinical application.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays.

- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO and oncology space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

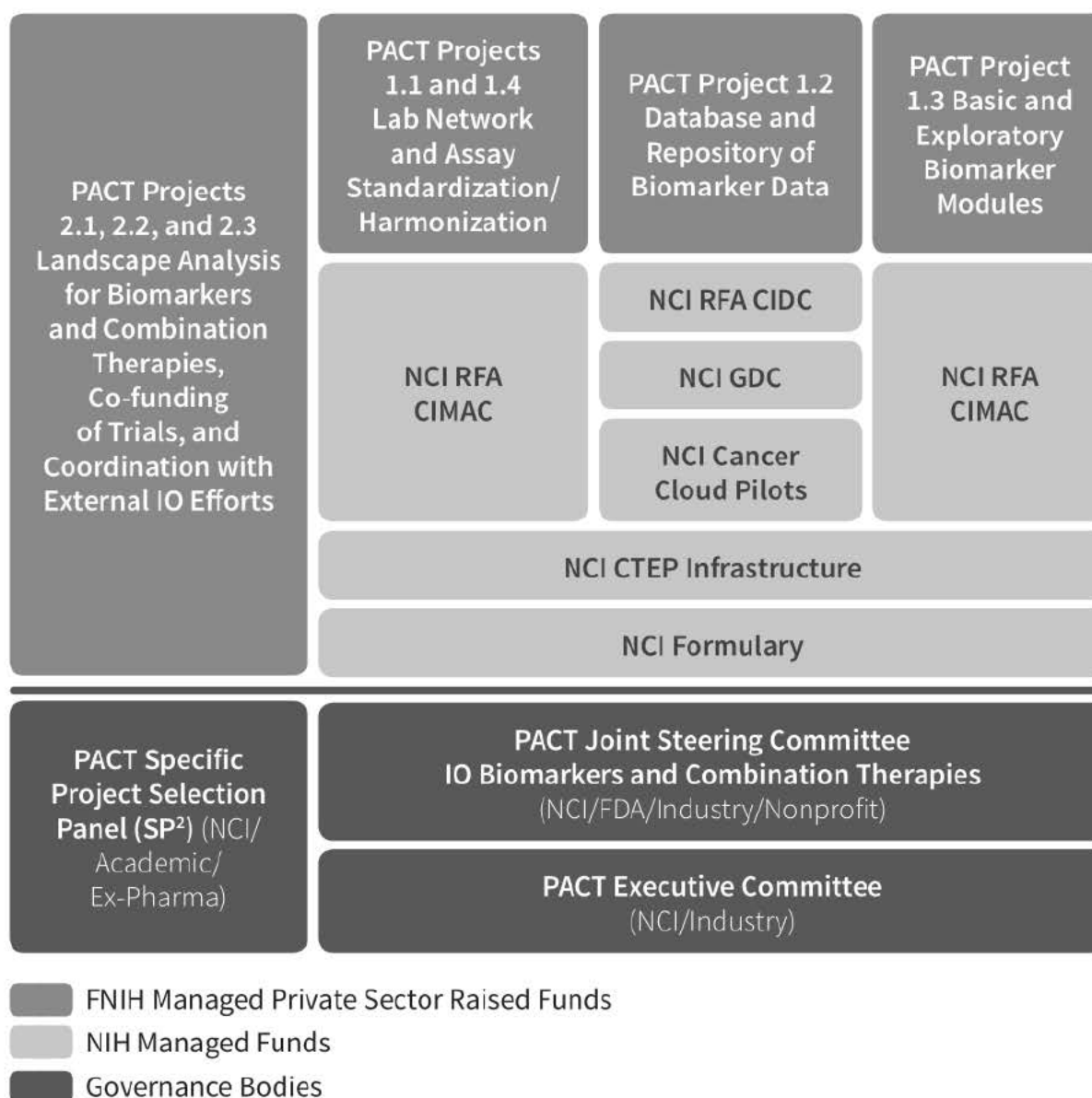
The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortuitously, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see **Appendix 5**). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

The additional ~\$141 million/5 years required to meet the baseline PACT goals will be raised through FNIH. A majority of these funds will be used to supplement NCI grants, although funds may be disbursed directly through FNIH contracts where appropriate. Additional funds may be sought later for future projects of interest to further PACT partnerships and goals.

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- ▶ An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- ▶ A PACT Scientific Project Selection Panel (SP²) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- ▶ A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.



Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH's mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data; however, data will be retained for analysis and not released publically until study analysis is complete and closed to accrual and treatment in concert with our research agreements for a reasonable time.

The **value proposition** for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- ▶ Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- ▶ Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- ▶ Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- ▶ Opportunities to initiate high relevance trials with company assets for PACT co-funding
- ▶ Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

Introduction

Over the last decade, cancer treatment options have substantially improved, now offering the prospect of greatly enhanced outcomes prolonged survival or cure for some patients. To date, such outcomes are only possible for a minority of patients; however, there is significant potential to expand this benefit to a broad majority of patients in many cancers.

Recently, the positive clinical outcomes associated with progress in cancer treatments have largely been driven by IO agents, which stimulate the immune system to eradicate or control cancer cells. The success of IO therapies in the treatment of melanoma, renal cell carcinoma, NSCLC, as well as some rare tumors such as Merkel cell tumors and Hodgkin's lymphoma has led to a rapid explosion of investments in IO research by the pharmaceutical industry, academic institutions, government, and nonprofit organizations. IO's greatest impact on cancer treatment is expected from combination therapies involving both multiple IO and complementary non-IO agents and will require systematic investigation of a large spectrum of new agents across the portfolio boundaries of individual companies. Despite the great resources invested in IO and related combination regimens to date, the task is complicated by high biologic complexity, the need for translational biomarkers to direct therapy, and the deeply competitive nature of the field, which has led to some redundant research and development efforts, duplication of costs and resources, and the absence of systematic approaches to scientific investigation.

To achieve the desired improvement in outcomes for a majority of patients, a systematic effort across a complex spectrum of pharmaceutical, biotech, academic, government and nonprofit stakeholders is required to effectively test therapeutic combination options and identify biologic markers that direct the right treatment combination to the right patient. This idea has long been gaining followers in the IO field and potential methods for addressing it have been laid out by key scientists in the field (Hoos, Britten, Huber, & O'Donnell-Tormey, 2011). However, the magnitude of this task and the substantial knowledge gaps that still exist make it unlikely that any single stakeholder can execute the task alone. A public-private research partnership such as PACT offers a unique opportunity to address this challenge by coordinating resources across NIH, FDA, biopharmaceutical companies, and patient groups using a focused, collaborative approach. PACT aims to accelerate progress toward improved outcomes by facilitating and enabling critical investigations not covered by others, thus filling knowledge gaps and integrating information from multiple sources across the cancer research sphere.

PACT will establish two program areas that will help determine high priority combination therapies and biomarkers (to be tested by PACT and others in the IO field) and generate the knowledge needed to reduce the number of unnecessary combination trials and improve patient participation in such trials.

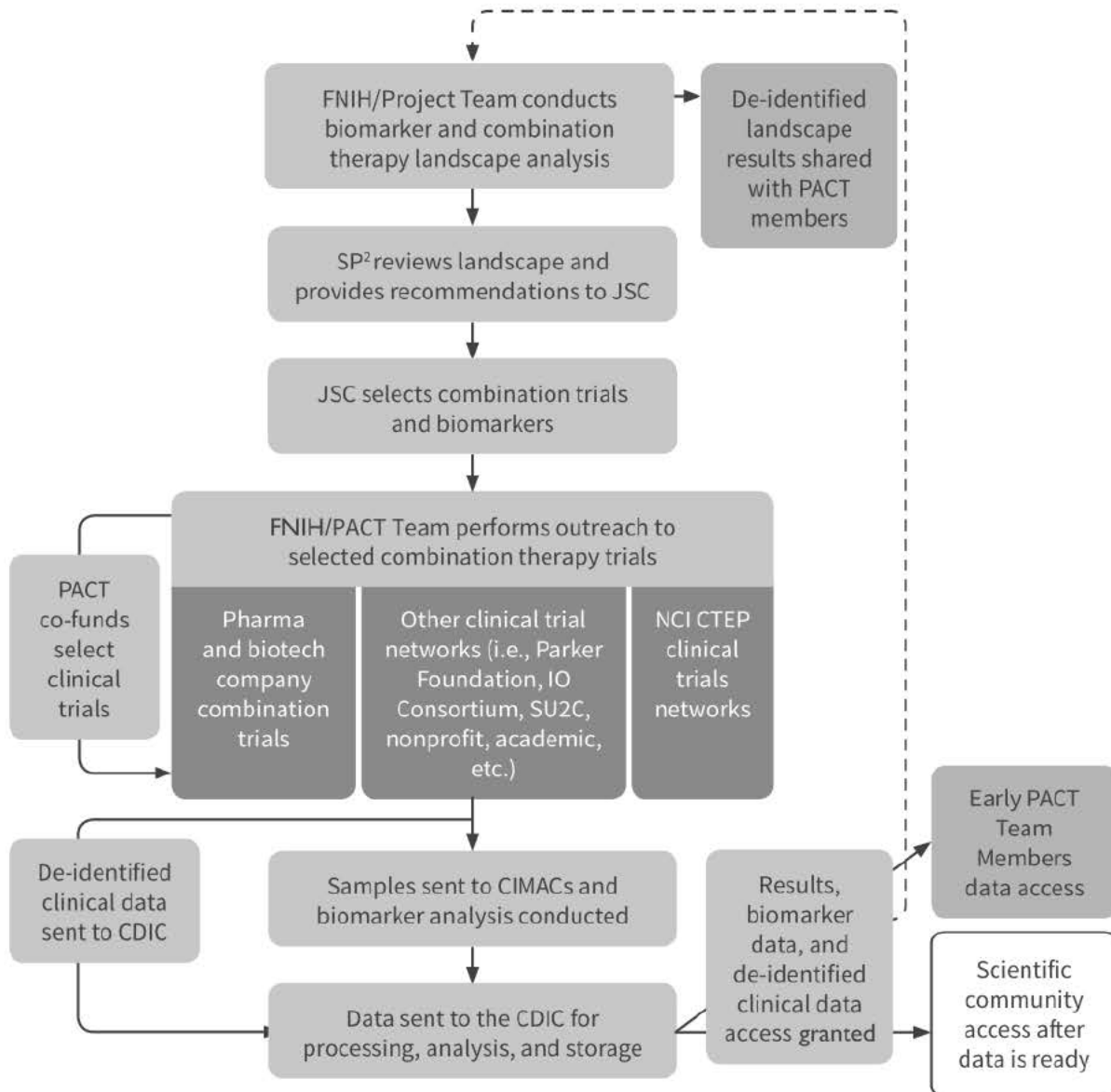
Program Area 1 will facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to

immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- ▶ Providing standardized biomarker modules for uniform clinical application across the community.
- ▶ Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays and data collection standards.
- ▶ Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- ▶ Incorporating biomarkers into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- ▶ Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program Area 2 will provide scientific coordination for the selection of clinical combination therapy trials important to oncology but not already being performed elsewhere, and co-fund a carefully selected subset of such trials with partners. This will be accomplished by the following:

- ▶ Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO space, enabling categorization of prospective new trials based on relevance.
- ▶ Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as trial networks) made by the government, companies, and nonprofit foundations.
- ▶ Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.



Value Proposition

The value proposition for participating stakeholders in PACT will be considerable:

- ▶ Access to an infrastructure for incorporating standardized immune biomarker modules in clinical trials, enabling a systematic analysis approach across trials, with reproducible assay results, reduced costs and resources, and enhanced power of correlative analysis
- ▶ Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, also relevant to potential registration and labeling
- ▶ Access to a comprehensive database for pre-competitive correlative biomarker analyses, accelerating data acquisition and hypothesis testing, and enhancing decision-making
- ▶ Enhanced reliability and speed of clinically relevant biomarker identification for identifying patients who will benefit from specific immunotherapy agents or combinations
- ▶ Opportunity to be the first to initiate a high relevance trial with the company's asset of interest, co-funded by PACT or its partners (e.g. NCI)
- ▶ Access to and participation in the coordination of clinical and translational programs across organizations in the IO space (pharmaceutical companies, biotech, academia, government, and nonprofits) to align investigative approaches, avoid duplication of effort, share/preserve resources, and thus allow for more relevant trials to be conducted
- ▶ Access to and participation in the creation of an up-to-date clinical trial landscape analysis for combination therapies across the entire IO space, including access to information about relevant investigations not yet covered by any party.
- ▶ Contributing to the goal of the U.S. Cancer Moonshot Initiative of doubling the rate of progress in cancer research and delivering more cures to patients
- ▶ Opportunity to drive new collaborations resulting from the insights of the PACT partnership

Program Area 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies

Objective

To reach the next level of benefit of immunotherapy for a broader number of patients, it is necessary to understand and characterize the complexity and dynamics of the immune state in cancer patients and the therapeutically induced changes in immune profiles in the tumor and the periphery.

Experimental findings point to the value of biomarkers for cancer immunotherapy in predicting benefit of therapy and understanding the mechanisms of resistance. For example, high tumor expression of PD-L1 is predictive of increased likelihood of clinical benefit from anti-PD-1 monotherapy in patients with NSCLC. Other factors associated with response include high mutational load, inflammatory gene signatures, and tumor-infiltrating lymphocytes. More recently, tumor genomic studies in patients treated with checkpoint inhibitors have revealed mutations in interferon response pathway genes as a potential mechanism of primary or acquired resistance. While these results are promising, systematic testing in larger patient cohorts is needed to confirm preliminary analyses and clinically validate predictive biomarker candidates.

PACT will provide the foundation for harmonizing the use of biomarker assays, data collection, and data banking, as well as optimize systematic biomarker incorporation into clinical trials to understand response and resistance to cancer immunotherapies and to enable new treatment strategies. Specifically, projects under Program Area 1 will address a few key challenges: inconsistent analytical validation standards and assay methodologies across trials, limited power of individual trials, and lack of common data platforms for combined analysis and cross validation across trials. Project 1.1 lays out the biomarkers the PACT team proposes to systematically incorporate into clinical trials as standard practice, while Projects 1.2, 1.3, and 1.4 detail the infrastructure that will be established to evaluate these proposed biomarkers in clinical trials.

Project 1.1—Establishing biomarker modules for systematic and uniform biomarker testing in clinical trials (for PACT and non-PACT studies)

Challenge/Opportunity

The lack of validated biomarkers and the current inability to compare data between clinical trials is a major challenge and partly driven by the absence of uniform and systematic biomarker investigation. This also limits the selection of the most appropriate immunotherapy regimen (single agent or combination therapy) for a given cancer patient based on validated markers. The fundamental lack of understanding of mechanistic interplay between the tumor and human immune system is a major hurdle for patient selection in IO/oncology clinical trials. Lack of data sets that encompass the molecular characterization of the tumor microenvironment (TME) correlated with clinical outcomes needs to be evaluated in appropriately sized patient data sets with a well-defined statistical analysis plan. Moreover, pharmacodynamic biomarkers can provide an early understanding about performance of a new agent or new combination, accelerating decision-making and prioritization. Comparable data sets from most trials conducted by stakeholders in the community, which close data gaps and allow for more systematic analyses, are needed to build validated biomarkers and truly effective patient selection strategies.

Solution

The PACT initiative will select biomarkers that are relevant to the testing of IO agents in clinical trials and that will help researchers to understand key biologic processes and to optimize decision-making in the application of existing and novel therapeutics. Biomarkers will be grouped in “modules”, a set of studies or analyses built around specific biological topics or areas of inquiry (for example, immune cell biology or liquid biopsies). Modules will fall into two categories: basic and exploratory.

Basic modules address commonly used or known biomarkers which can be reliably tested by a broad spectrum of clinical trials. They are fundamental to investigating specific aspects of cancer biology and building baseline data for how immunotherapy treatments effect this biology, have current clinical utility, and should be executable by the majority of trial sponsors in the oncology field. Basic modules must be usable by a majority of investigators. They are meant to be broadly applicable to most trials and still deliver insights for specific trials.

Exploratory modules will test novel or less well-established markers), and represent an expansion into new areas of science or technology which need further validation or which PACT participants may not be positioned to (or not desire to) study on their own. They are meant to address a specific biology question of interest relevant to each specific trial. Exploratory modules can be added to PACT on an optional basis until enough evidence consistently demonstrates their relevance and applicability so that they can be considered basic standard biomarkers. The exploratory biomarker modules will accommodate new scientific and biomarker discoveries and advances to be introduced and tested by a few investigators initially. Exploratory biomarkers

can cover all types of new assays being developed for tracking treatment response, including imaging, sequencing, proteomics, immunohistochemistry (IHC) multiplexing, and single-cell analysis.

Modules are expected to be used as follows:

1. All PACT-associated studies will be required to test PACT basic biomarker modules—i.e., meaning each study participating in PACT will need to run the basic modules.
2. NCI will adopt PACT biomarker module recommendations for all NCI studies whenever feasible. These efforts will be synergized with the assays being selected for the CIMAC laboratory network.
3. PACT partners and collaborators will be asked to use PACT selected biomarkers with the aim to standardize and harmonize data generation and collection in studies outside of PACT. The use of these biomarkers can either be through the use of the CIMACs or through use of standardized protocols. The process of selecting these non-PACT, external trials to use the CIMACs will be facilitated through the Scientific Project Selection Panel (SP²) and the Joint Steering Committee (JSC).

Each basic biomarker module will employ comparable methods across all participating medical centers and trials. Such comparability will require selection of assays with similar specifications and harmonization of the assays used across participating centers. If achieved, this will allow the cross comparison and coordinated analysis of data across multiple trials.

In addition, the PACT initiative will need to identify clinical trials from which standard biomarkers and/or samples can be collected that can be used to characterize or validate novel Exploratory biomarkers. PACT will place emphasis on identifying combination therapy clinical trials where collecting biomarker information is a high priority to the IO community. The understanding of the mechanisms of response and resistance to IO therapies that will result from the biomarker analyses will aid in the further refinement and selection of combination therapies for future testing.

PACT will not establish its own clinical trials network infrastructure or fully sponsor trials itself, but will partner with and utilize existing clinical trials networks, such as the NCI's National Clinical Trials Network (NCTN) and Experimental Therapeutics Clinical Trials Network (ETCTN), or networks established by nonprofit organizations or industry sponsors. The SP² will identify these trials based on the periodic landscape analyses that will be conducted as part of PACT and pass their recommendations to the JSC. The JSC and the PACT outreach team can work with these external networks or sponsors to help broker a partnership with PACT on those trials resulting in eventual deposition of the relevant biomarker and clinical data into the common PACT database. PACT will also consider providing supplementary funding to conduct these trials in selected cases. This process for trial selection is further described below in **Program Area 2**.

Focus of the Project

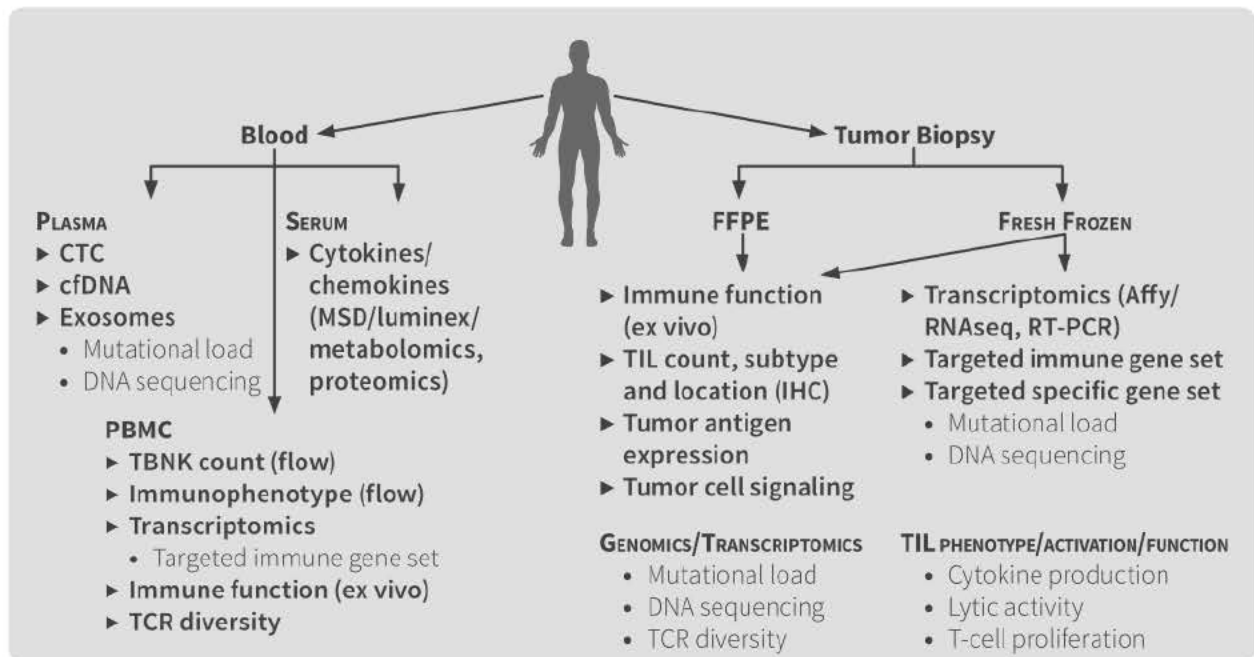
As described above, two types of biomarker “modules” will be pursued for PACT: basic and exploratory modules. Table 1 describes the modules defined thus far by the PACT Working Groups. This table is divided by basic and exploratory modules and defines what tissue collection will be necessary for each.

TABLE 1. PROPOSED PACT BIOMARKER MODULES			
MODULE #	BIOLOGY TO BE STUDIED	DESIRED ASSAYS	SAMPLE REQUIREMENT
BASIC			
1A	Immune cell biology	Periphery: Flow cytometry and CyTOF—3 (T and B cell panels) Tumor: IHC	Blood, tumor biopsies (core and bulk)
1B	Peripheral cytokines/chemokines	ELISA	Blood/serum
2A	Cancer genetics / somatic mutations	Whole exome sequencing (100X coverage—per standard practice)	Tumor biopsies (core and bulk), blood— isolated DNA 200-500 ng
3A	Transcriptomics of the tumor microenvironment	RNA-seq (150 million reads/sample)	Tumor biopsies (core and bulk), blood
4A	Liquid biopsy	cfDNA assay	Blood— Streck or EDTA tube
EXPLORATORY			
1c	Immune cell biology	Expanded flow cytometry (innate immune cell panels)	Tumor biopsies (core and bulk), blood
2B	Cancer genetics / somatic mutations	CNVs, SNPs, T and B cell deep receptor sequencing	Tumor biopsies (core and bulk), blood
3B	Transcriptomics of the tumor microenvironment	Single cell/nuclei RNA seq, others TBD	Tumor biopsies—single cell isolates, blood
4B	Liquid biopsy	CTC, cfRNA, exosomes, microvesicles, others	Blood—collection tubes TBD
5	Defining the microbiome	Microbes and others (see section below)	Stool, saliva, others TBD
6	Non-immune tumor architecture	IHC, IF, others TBD	Tumor biopsies (core and bulk)

Basic biomarkers will be standard and mandatory for all PACT biomarker analyses, subject to the sample collection limitations for each trial; exploratory biomarkers will be optional. Biomarkers selected for the basic modules will be harmonized with the assays and platforms named in the CIMAC RFAs. The PACT team has established the priority ranking for mandatory modules: 1a > 2a > 4a > 3a > 1b. Exploratory modules can be conducted at the discretion of PIs; however, if these modules are run, the data generated should be captured in the PACT database. The consistent acquisition of such data across all PACT-related studies will constitute a major advance.

Common Tissue Collection Needs for Biomarker Modules

Any biomarker investigation is only as good as the quality of human samples collected and the reproducibility of the assays used. PACT intends to address both of these issues through careful collection and standardization of biomarker assays. An initial schema for biomarker testing has been outlined as follows:



Baseline Tumor, During Treatment, and Post Treatment (When Possible):

- ▶ Bulk tumor resection (fresh)
- ▶ Core biopsy materials
- ▶ Blood
 - ▷ Standardized whole blood and plasma collection (optional banking protocol)
 - ▷ EDTA tubes, Red top serum tubes, CPT tubes with sodium heparin, and others
- ▶ Bone marrow for hematologic malignancies

- ▶ Standard tissue processing procedures
 - ▷ FFPE
 - ▷ Snap frozen—referred for DNA extraction
 - ▷ RNAlater
 - ▷ Single cell suspension
 - Tissue process with or without enzyme digestion
 - Cell freezing media and standard operation procedure
- ▶ Standard operating procedures (SOP) for dual extraction of DNA and RNA if possible should be explored
 - ▷ Isolated DNA necessary for samples for WES—200–500 ng
- ▶ Emerging tissue processing approaches
 - ▷ Single nuclei recovery for RNA-seq
 - ▷ Smart Tube system for flow cytometry (<http://smarttubeinc.com/index.htm>)
- ▶ Potential biomaterials for microbiome sampling
 - ▷ Serum
 - ▷ Mucosal (Oral swabs, endoscope)
 - ▷ Urine/Fecal
 - ▷ Tumor

Tissue Collection

It is anticipated that tissue collection including blood draws, biopsies and other specimen collections could cost up to \$5,000/patient/time point, if specimen processing is included in the estimated costs. The PACT team anticipates this cost will likely be covered by the groups sponsoring the trials, and that PACT would support the actual conduct of the biomarker assays in the CIMAC laboratories. As a potential optional incentive for trials to participate in PACT, the PACT team could choose to subsidize this cost for trial sites; however, this would need to be a buy-up option, and PACT would likely not be able to support the full \$5,000. This is therefore listed in the budget as a buy-up option at \$7.5 million over 5 years.

Establishing a Biospecimen Repository

Establishing a biospecimen repository will be necessary to allow for easier centralized storage, processing, and accessioning of samples for those trials where further biomarker assays maybe required or desired in the future. This will be especially critical for PBMCs, cfDNA, and other liquid biopsy assays, where a given trial may want to store samples for batch runs or for development of future assays and technologies. Two clear models for biobanking could be established:

- 1) decentralized sample collection, with centralized storage, and centralized database/informatics and
- 2) decentralized sample collection, with decentralized storage, and centralized

informatics. PACT proposes to follow the second model, since PACT trials will be run by multiple organizations, and there will likely be a need to allow the industry trials to retain possession of samples from the trials that they exclusively fund but use PACT biomarker modules or PACT core laboratories. However, PACT will, where possible, recommend that centralized storage also take place.

One option for utilizing existing infrastructure for centralized storage would be to use existing biospecimen repositories at NCI. Both the NCTN and the ETCTN already have biorepositories, and private funding could be used to supplement the grants that already sponsor these repositories. Regardless of where the specimens are stored, the PACT effort will require a centralized accessioning of the samples for initial processing before being sent to the CIMACs for processing. This will allow for accurate tracking of all biospecimens that are part of the PACT effort and could potentially be used for future testing.

Biospecimen Repository Expansion Budget

Supplementing the existing biospecimen repositories at NCI will likely cost ~\$1 million to \$2 million per year to process, accession, and store the samples for the potential 720+ patient samples that are currently due to be collected as part of the CIMACs or external trials. This number would increase if the number of patients were to scale up. This means that a total of as much as \$10 million over 5 years would be necessary for this effort. If PACT were to establish an independently run biorepository, the cost would likely be much greater than this amount. Therefore, \$10 million dollars over 5 years has been added to the PACT budget estimate (see the table at the end of this section.)

1.1.1—Basic Modules

The PACT team had proposed that IHC/flow cytometry (depending on tumor type) and DNA sequencing should be the top priority modules. RNA-seq should be a second priority, unless a particular study mandates a need for this assay. These core modules were selected by the PACT team because they provide a solid knowledge base for cross-comparison of clinical trials that are testing IO therapies. In addition, these modules are well developed and offer good options for standardized assay platforms, as well as analysis techniques. However, a common platform for each module will still need to be selected as part of the research plan for this project for PACT. Platforms and analysis techniques will be selected by the JSC in consultation with the CIMAC team.

Focus of the Project

Mandatory biomarkers will be prioritized by tissue availability and trial needs, but the mandatory modules run for PACT will be standardized across all trials. This means that for some trials not all modules will be used, so PACT has ranked the assays based on amounts of tissue (see above).

Biomarker Module 1: Immune Biology

Focus of the Project

Module 1 is organized into two categories of focus: peripheral samples (i.e., circulating soluble or cell-based biomarkers) and tumor samples. Samples of peripheral blood and resection or biopsy of tumor tissue will be collected, and broad testing is planned.

Module 1a: Immune Cell Biology

Peripheral Specimens

Peripheral samples of blood, serum, or plasma should be collected at multiple time points throughout the course of treatment to allow for longitudinal evaluation of changes in immune biology and, if possible, to correspond with measures of drug exposure. These time points and sample sizes will be dictated by individual clinical protocols. Assays for characterizing the functionality of immune cells by in vitro stimulation can also be developed and will constitute the third flow cytometry panel for Module 1a basic biomarkers.

To analyze peripheral samples, the most common technologies used are flow cytometry and CyTOF for cell based analyses and ELISA-based methodologies for measurement of soluble markers. For a basic evaluation of immune cell biology in the periphery, the panels listed below in Table 2 are recommended. In addition, markers of functional characterization of isolated PBMCs are shown.

TABLE 2. T CELL MARKER PANELS BY FLOW CYTOMETRY

ACTIVATION	EXHAUSTION	FUNCTIONAL
LIVE OR DEAD	LIVE OR DEAD	LIVE OR DEAD
CD3	CD3	CD3
CD4	CD4	CD4
CD8	CD8	CD8
CD45RO	CD45RO	IFN γ
CD69	LAG3	TNF α
ICOS	TIM3	GZMB
OX40	CD161	IL-2
FOXP3		
CD127		

In Vitro Functional Characterization of PBMCs

- Ag recall
- Epitope spreading
- MLRs

Tumor

Obtaining multiple samples of tumor tissue must be attempted throughout the course of a patient's treatment to allow for longitudinal evaluation of immune response depending upon the needs of the protocol.

Tissues will be collected by resection and/or biopsy. These samples can be fixed, frozen, or used immediately for IHC, gene expression, and TIL analyses (by flow cytometry). Similarly, TILs, once isolated and if sufficient, can be used for in vitro stimulations for cytokine analyses. Specific protocols for sample collection and assay execution are to be defined. For the IHC-based assays, standardized quantitative imaging analysis methodologies will be developed. For flow cytometry-based assays, standardized methods for cell gating will be employed. Tissue is less readily available at multiple sampling points and will be prioritized for use in testing for biomarkers. Evaluation by multiplex IHC will take precedence over flow cytometry and in vitro analyses of immune function, as the recovery of isolated TILs from biopsies may not be sufficient. An example basic panel for IHC is shown in Table 3.

TABLE 3. MARKERS (IHC)

CD3	CD16	PD1
CD8	CD56	MHC-1
CD45RO	CD19	TIM3
CD4	CD68	LAG3
FOXP3		

Value Proposition

Data from this module will add to the overall information to understand mechanisms of action for the intervention, mechanisms of therapeutic sensitivity and resistance, and patient selection leading to efficacy.

Approximate Module Budget

Periphery: This estimate is based on a six panel flow analysis, including a measure of receptor occupancy, which should be ~\$2,500–\$3,000/sample. However, this cost may be reduced if we are able to use bulk rates and synergized cost structures within the CIMACs network.

Tumor: This estimate is based on using a simple or single biomarker IHC approach. It should be noted that this approach uses the most tissue.

The cost for this analysis will be ~\$250–\$300/marker. The total cost for the panel is approximately \$3,250–\$3,900/sample. An alternative approach will be to generate multicolor IHC panels that will lead to less utilization of tumor tissue and may provide a moderate cost improvement.

Module 1b: Cytokines/Chemokines Periphery

Multiplex cytokine evaluations using one of the several ELISA-based platforms, such as Mesoscale, ELISA, or Luminex, will be used to test several circulating cytokines in the plasma/serum. The markers will include mediators of immune activation, inflammation, target cell killing, and safety signals such as those of the cytokine release syndrome shown in Table 4.

TABLE 4. SOLUBLE FACTORS

G-CSF	IL17	GZMA
GM-SCF	IL2	GZMB
IFN γ	IL4	PERFORIN
IL1	IL6	CCL2
IL10	CXCL2	CCL3
IL12	IL7	CCL8
IL13	M-CSF	CCL5
IL15	TGF β	CX3CL1
IL16	TNF α	CXCL10 (IP-10)
IL21		CXCL9 (MIG)

Multiplex Immunoassays**► Immune activation**

- Cytokines
- Chemokines
- Inflammatory mediators

► Safety

- CRS-targeted panel

Approximate Module Budget

This estimate is based on a 29-panel multiplex ELISA-based platform which will be ~\$500–\$600/sample, depending on the choice of platform.

Module 2a: Cancer Genetics/Somatic Mutations

Advances in genome sequencing technologies at affordable cost along with progress in bioinformatics has propelled the field of somatic cancer genetics into a new era. The exponential growth of cancer genome datasets has been justified as a means to identify new cancer genes and pathways that could be the basis for molecular classification of tumors, initiate novel target-based drug discovery programs, and perform molecular profiling of tumors to match therapies with patient-specific genetic alterations. The relevance of mutated antigens in the field of tumor immunology (Gilboa, 1999) has been corroborated by studies of patients receiving checkpoint inhibitors that reported significant clinical benefits correlating with mutational and neoantigen loads (Miao & Van Allen, 2016; Rizvi et al., 2015; Snyder et al., 2014). In addition, tumors with a large number of somatic mutations due to mismatch-repair defects have been shown to be susceptible to immune checkpoint PD-1 blockade therapy (Le et al., 2015). The basis for this correlation is that an increased number of mutations will increase the number of neoantigen specific T-cells capable of eliciting a strong immunogenic response; the very checkpoint blockade that impedes the tumor's ability to suppress neighboring T-cells results in an increase in tumor-cell killing in the presence of a highly immunogenic tumor.

Focus of the Project

To continue to expand on this somatic mutation knowledge and assure that it can be leveraged to determine novel genetic biomarkers related to immunotherapy, the PACT team proposed to conduct whole exome sequencing (WES), taking into account the following principles.

Matched normal tissue: In order to ascertain whether a sequence variant found in a tumor is somatic or germline, it is necessary to sequence normal DNA from the same individual. While tumor-only WES data can be compared to large germline databases to infer whether a mutation is somatic, false positive calls are frequent, particularly in ethnic populations (Garofalo et al., 2016).

Sequence coverage: Mutation load and predicted neoantigens have rapidly emerged as standard biomarkers used in IO trials. The current gold standard laboratory assay for measuring mutation and neoantigen load is whole exome sequencing (WES; $n \approx 20,000$ genes), as opposed to whole genome sequencing (WGS) that provides additional information regarding noncoding somatic mutations that do not produce neoantigens. WES is therefore more cost-effective for immune-oncology purposes. Given that clinical genomics laboratories that are hospital-based or commercial more commonly use gene panels that cover dozens to hundreds of genes, questions have arisen whether these could be adequate for immunotherapy purposes. Dr. Garofalo and colleagues performed comparisons of gene panels with WES. Mutation loads were estimated using large ($n=300-500$) gene panels and were shown to correlate with WES mutational load above a certain cutoff, although by virtue of the limited sampling of human genes contained in gene panels, the vast majority of neoantigens could not be detected. Therefore, it may be concluded that gene panels are substantially inferior to WES in predicting neoantigens (Garofalo et al., 2016). For cost efficiency purposes, PACT will infer trunk versus branch mutations via allelic frequencies from a single tumor site versus multiple tumor sections.

Mutation calling: A recommended approach in the context of multicenter and multiyear clinical studies is to store raw NGS data files in secure databases and reanalyze all data simultaneously using a validated and harmonized pipeline to allow robust analyses of mutation and neoantigen loads with clinical and other data.

Copy number alterations (CNAs): CNAs, which include gains and deletions of DNA segments, can be detected using clinical WES (Rennert et al., 2016). While the relevance of CNAs in predicting the efficacy of immunotherapies is generally less understood, there are reports of specific CNAs correlating with immune phenotypes, and it will be informative to correlate CNAs with other immune markers.

Neopeptide prediction algorithms: Combined use of multiple tools likely gives a better prediction; however, more efforts are needed to accurately assess the immunoprotective properties of neopeptides.

Approximate Module Budget

This estimate is based on analyzing both tumor and normal samples from each patient.

The WES assay cost is \$500–\$1,100/sample (100x coverage, depending on the number of GB). The cost per patient may be estimated at \$2,200 if one assumes 100x WES with 9 GB. The PACT JSC will need to select the optimal coverage to cost ratio that will be acceptable for the WES Basic biomarker module.

Module 3a: Transcriptomic Characterization of Microenvironment

Transcriptional programs in the tumor microenvironment are an important downstream marker of biological processes such as T-cell activation with reported gene expression profile (GEP) signatures including Type I interferon, interferon gamma, T-cell exhaustion, Th1, as well as the cytolytic activity score. Signatures of extrinsic immune suppression such as IDO-1 or TGF-beta expression highlight mechanisms in addition to immune checkpoint blockade that may overcome resistance through combination therapy. In addition to signatures in tumor, pharmacodynamic changes in immune gene expression signatures in blood have been shown to correlate with response to treatment. Approaches to measure mRNA expression span low complexity techniques including qRT-PCR as well as medium complexity technologies such as TaqMan, Nanostring, Luminex, and targeted NGS panels via hybridization capture or PCR amplification, as well as genome-wide RNA sequencing. Several GEP signatures predictive of patient response to treatment have been reported: NanoString signatures in tumor have correlated with clinical outcome in patients treated with PD-1 blockade (Cesano, 2015; Geiss et al., 2008; Man Chow et al., 2016; Piha-Paul et al., 2016; Ribas et al., 2015). Whole transcriptome profiling provides the opportunity for genome-wide characterization of the TME.

Focus of the Project

The PACT team proposes to perform systematic RNA-seq at a depth of 150 million reads across all tumor samples.

In addition to profiling the primary tumor prior to treatment, profiling samples during treatment or upon relapse provides insight into mechanisms of resistance, and point to attractive combination opportunities; it is therefore suggested for those tumor indications where sequential biopsies are possible.

Value Proposition

Transcriptional read-outs of individual malignant and nonmalignant cells from tumor tissue may offer additional insights into cellular states and programs (and heterogeneity therein) that may influence response or resistance to cancer immunotherapies/combinations.

Through supervised or unsupervised learning, GEP modules can be identified and correlated with important clinical outcomes such as prognosis or response to treatment. There are ongoing clinical trials using NanoString GEP signature prospectively to triage patients for different immunotherapies. Novel genes that are co-expressed with established gene expression

signatures can identify new targets and illuminate unknown biology. Fingerprinting approaches can be used to deconvolute immune subpopulations. The expression of candidate neoepitopes can be investigated, as well as effects on alternative splicing.

Approximate Module Budget

The cost of these assays range from ~\$1,000–\$3,000, depending on the platform used for sequencing, the depth of coverage requested, and the type of RNA to be analyzed. Depending on the sequencing facilities and the number of samples to be analyzed, the average cost for a 150 million read standard RNA-seq should be approximately \$1,500/sample. This would make the estimated cost/patient ~\$1,500.

Module 4a: Liquid Biopsy - cfDNA

The difficulty in acquiring routine tissue biopsies in the solid tumor setting hinders the ability of a clinical laboratory to provide real-time information to clinicians and convenient options for patients. Advances across multiple areas—sample preparation, next generation qPCR and sequencing capabilities, rare cell detection and analysis, ultra-sensitive protein detection, storing, accessing, and analyzing very large data sets—are enabling unprecedented multi-dimensional data collection. Liquid biopsy for solid tumors is currently being used, but the complexity of integrating data across cfDNA, exosomes (includes profiling mRNA, miRNA, lncRNA, proteins, etc.), and circulating tumor cells poses a challenge to exploit the full potential of this approach. Moreover, advances in liquid biopsy technologies are occurring much more rapidly than clinical validation of these assays.

Focus of the Project

Biomarkers will be driven by the clinical questions asked. While it is not realistic to propose all possible clinical settings, it is highly likely that immunotherapies will continue to be combined with other targeted agents and therefore biomarker testing will reflect the combined mechanisms of action of all agents. For instance, in nonsmall cell lung cancer, EGFR mutations and ALK fusions will still be tested even as immune-related biomarkers are adopted. For this module, we are proposing a common approach in the pre-analytical phase of testing that will allow for better comparison of analytical testing platforms chosen by individual research teams.

NGS-DNA-seq will be the primary experimental screening platform, which is good for biomarker discovery/research, LDT approaches, and is also the preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies).

Value Proposition

Testing specimens derived from relevant body fluids (e.g., blood, CSF, pleural fluid, etc.) that may reflect various aspects of tumor pathobiology could better enable clinical decision-making and provide for surrogate endpoints. It could also allow for broader immunoprofiling of patients at more time points before and after IO therapy. This ability to track data from IO treated patients longitudinally and more frequently will allow for more rapid development of novel IO-related biomarkers for treatment development and efficacy. PACT proposes as its basic biomarker module for liquid biopsy to conduct mutation analysis in cfDNA. Specimens for this assay and

other liquid biopsy options can be banked in a biospecimen repository for future processing. Again, this can provide for greater ability to immunoprofile patients using assays developed in the future.

Approximate Module Budget

The cost of this assay will be determined by the cost to collect and process the cfDNA, as well as the costs for the NGS-DNA-seq. The appropriate depth of coverage will need to be selected based on the clinical needs. A safe estimate may be ~\$1,100/sample to align with the WES costs from the DNA module. However, costs could be higher depending on the sequencing coverage required to find the desired mutations in the low amount of DNA present in these samples. The appropriate cost to coverage ratio will need to be determined by the JSC.

Value Proposition for the Basic Modules

Selecting a set of high importance, broadly applicable, and widely testable biomarkers that can be conducted for every PACT-related clinical trial will allow for the systematic cross comparison of IO therapy trial data on a much grander scale than is currently possible. This will allow novel precompetitive predictive biomarkers to be developed for IO therapies of various classes. The ability to cross-compare trials will also allow for complex modeling studies to be conducted to aid in the prediction of better therapy combinations. There are several key questions in the advancement of IO therapies that the biomarkers proposed by this initiative can attempt to answer. These include target engagement, pharmacodynamic activity, mechanisms of sensitivity and/or resistance, as well as identifying the most appropriate patients to treat based on risk/benefit criteria with individual agents or combination therapies. The value of having the data from all of these standardized assays for multiple clinical trials will be to accelerate the discovery of new immunoprofiling markers that can be used to hasten the approval for novel therapies.

Approximate Budget for Basic Modules

The current cost estimations for all the Basic biomarkers, including 3 peripheral flow panels, 1–2 basic IHC assays, WES, and RNA-seq for each patient, range from \$10,000–\$14,000 per time point. (Note: this is greater than the current estimated cost per patient for the CIMACs testing, which is ~\$8,000–\$10,000/sample.)

1.1.2 - Exploratory Module/Assay Development (Buy-up Options)

Evaluation of exploratory biomarkers may also can be performed depending on availability of samples from the periphery and tissue and the specific objectives of the relevant clinical trial. Various stakeholders (e.g., NCI or a company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies. Importantly, exploratory biomarkers or novel assays are necessary for the continued evolution of the biomarker space and can graduate to become part of basic modules once better established. The proposed areas for exploratory marker development are listed below and described in detail in **Appendix 1**.

- ▶ Module 1c: Immune Cell Biology
- ▶ Module 2b: Cancer Genetics/Somatic Mutations

- ▶ Module 3b: Transcriptomic Characterization of Microenvironment
- ▶ Module 4b: Liquid Biopsy—CTC, cfRNA, exosomes
- ▶ Module 5: Defining the role of the microbiome in modulating CI responses
- ▶ Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (differentiation, stroma, vasculature, etc.)

Value Proposition for the Exploratory Modules

Allowing expansion assays to be options for buy-ups for the PACT initiative will allow both the NCI and private sector to fund the development of additional assays that can then be validated to become basic modules that can be incorporated into future clinical trials. This will allow PACT to drive innovation of new IO biomarker development and allow end users to weigh in which biomarkers which markers should be developed. The value of executing these modules through PACT lies in the breadth of use of the markers that can be achieved across the community and the ability to generate consistent data in every trial. The PACT JSC can select and fund desired modules using an RFA or RFP process that insures buy-in and participation of both PACT partners and external trial sponsors.

Approximate Project Budget for the Exploratory Modules

The cost for these expansion modules will of course depend on which assays are selected to be developed and tested. The assay cost will depend the current maturity of the technology, the biomarkers to be developed, and the expense to fully test and validate them. The PACT team estimates an RFA for new biomarker development in clinical trials would cost ~\$1 million to \$2 million per biomarker, which would account for collection of enough data to analytically validate a new biomarker and potentially harmonize it to any existing data if necessary. Assuming development of each assay cost the maximum \$2 million, PACT would hope to fund development of at least one biomarker per year over 5 years for an estimated total of \$10 million for the RFA.

Project 1.2 — Creating a core laboratory network for biomarker analysis

Challenge/Opportunity

Although diagnostic tools have significantly enhanced the depth and comprehensiveness of our abilities to characterize the tumor immune microenvironment, the current use and development of translational biomarkers are limited by insufficient resources for large-scale studies, variabilities in pre-analytic/analytic qualities and standards, and, more importantly, by a lack of common standards and platforms for biomarker data collection (especially for nongenomic “immune” parameters) and inadequate computational tools/platforms for complex, high dimensional analysis.

Consequently, at least three elements are critical to enabling optimized biomarker strategies:

- ▶ Access to biospecimens from early and late stage single agent and combination clinical trials that involve relevant immunotherapy agents
- ▶ Access to laboratory resources and assays with analytical validation and standardization appropriate for achieve clinical biomarker testing
- ▶ Availability of suitable, interoperable data repositories for clinical, genomic, and non-genomic data generated across disparate trials and organizations, similar to that provided by the NCI Genomic Data Commons

Solution

PACT proposes to build on the Research Funding Announcement (RFA) released by the National Cancer Institute (NCI) in November, 2016, to establish a **network of Cancer Immune Monitoring and Analysis Centers (CIMACs) and a Cancer Immunologic Data Commons (CIDC)**, in order to provide consistent, standardized biomarker assays and data repository for NCI's extramural clinical trial networks (links to RFAs in **Appendix 5**). The RFA is open to application from academia, nonprofit and for-profit organizations, and up to 3 CIMACs will be funded with a total budget of \$32.5 million for all 3 centers from NCI over 5 years starting 2017. Each CIMAC will encompass a multidisciplinary group capable of a wide range of analyses for genomic, phenotypic, and functional characterization of the tumor immune system using analytically validated and standardized platforms. The CIMAC-CIDC network will function in a coordinated manner through a central Core Laboratory Coordination (CLC) Committee. The capacity of the proposed CIMACs will provide the mechanism and basic infrastructure needed for objectives of **Program Area 1** of the PACT initiative.

- ▶ The CIMACs to be established through the RFA are budgeted to address the biomarker study needs of early clinical trials of immunotherapy that use the NCI clinical trial networks. PACT has the potential to leverage components of this infrastructure for PACT-prioritized studies. For example, PACT can add new capacity for specific assay platforms or expand the scope of biomarker work for more clinical trials and patients selected by PACT.
- ▶ The clinical trials for PACT-supported biomarker studies can be conducted through a variety of existing clinical trial infrastructures supported by NCI, academia, nonprofits, and industry.
 - ▷ For example, the NCI Cancer Therapy Evaluation Program (CTEP) has an extensive extramural clinical trial network for phase 0 to phase IV trials [including ETCTN, NCTN, the Cancer Immunotherapy Network (CITN) and the Children's Oncology Group (COG)]. CTEP provides standing support for centralized regulatory, data collection, drug distribution infrastructures, and clinical trial conduct in the network sites. CTEP also has a large portfolio of immunotherapy and targeted agents under its collaborative agreements with multiple pharmaceutical companies. Since 2010, CTEP has initiated more than 90 phase I to phase III trials for immunotherapy agents and novel combinations involving immunotherapy.
 - ▷ Other clinical trial mechanisms would also be appropriate for PACT-supported biomarker studies, such as academia, nonprofit funded immunotherapy consortia, and industry-sponsored trial networks.

- ▶ Private sector diagnostic and assay companies and laboratories will be eligible to compete to conduct certain assays for the CIMACs if the CLC determines that this is the most efficient way to conduct these tests.
- ▶ PACT will identify existing/planned trials or develop new trials using existing trial mechanisms and support the implementation of biomarker studies in order to address important scientific questions prioritized by the PACT JSC (as described in Project 2.1 and PACT Governance).
- ▶ PACT will facilitate and maintain close communication with industry, academia, and non-profits for their inputs in identifying opportunities and gaps, prioritizing scientific projects, and sharing expertise and resources where appropriate. This effort is delineated in Project 2.2, described below.

Focus of the Project

To support the goals of the proposed PACT Program Area 1, a network of reference labs will be identified for high priority assay platforms. These “core” biomarkers to be applied are described in Project 1.1. Depending on the stages of development of specific markers and the anticipated purposes of their uses in trials, varying degrees of analytical validation will be required (defined in Project 1.4).

Proposed services for biomarker studies may include quantitative and qualitative methods for immunoprofiling using phenotyping, functional analysis, genomics, epigenomics, transcriptomic, proteomics, metabolomics, or glycomics. Although Clinical Laboratory Improvement Amendment (CLIA)-certified assays are not required for all biomarker studies to be supported by PACT, the selected core laboratories should have the capacity to carry on validation steps from analytical to clinical validation for candidate markers and perform integral biomarker assays (for treatment eligibility) in a CLIA-compliant laboratory that may require an Investigational Device Exemption (IDE) from the FDA. Assay platforms to be employed by reference labs may include, but are not limited to:

- ▶ Multi-spectral flow cytometry, mass cytometry and imaging cytometry
- ▶ DNA-seq for genotyping of variants, T-cell clonality, relevance of T-cell and B-cell epitopes
- ▶ High-throughput transcriptional profiling, RT-PCR, NanoString, RNA-seq
- ▶ Pathological and morphological imaging techniques (e.g., confocal microscopy)
- ▶ Immunohistochemistry (IHC), multiplexed immunofluorescence

The scientific goals of the lab network are to search for patient/treatment selection markers and provide mechanistic insights into immunotherapy agents and combinations. In appropriately selected clinical trials, specific biomarker objectives may include, but are not limited to:

- ▶ Defining the role of inflammation and tumor microenvironment in response/resistance
- ▶ Phenotypic and functional characterization of the immune system, and its impact on response/resistance

- ▶ Functional genomics of tumor and host
- ▶ Identifying tumor target antigens, such as neoantigen, and responding host T-cell receptor repertoire
- ▶ Developing assays to guide rational selection of combinations in individual patients
- ▶ Longitudinal sampling to monitor dynamic changes and target modulation by drug (e.g., in combination therapy)
- ▶ Defining the role/impact of the human microbiome on response/resistance
- ▶ Exploring the mechanisms and predictive markers of immune-related toxicities

A few guiding principles will be followed in the selection of the reference laboratories:

1. The network of laboratories should have the collective capabilities to carry out comprehensive immune profiling assays and analysis on clinical specimens. Based on the current understanding of relevant biomarker platforms, core and exploratory immune biomarker modules are described in Project 1.1, although the lists of the two categories may evolve with time.
2. Depending on the stage of scientific and technical development, some markers will be best tested in individual labs (such as markers utilizing newly developed technologies, and exploratory biomarkers). Others will be developed within a network of qualified labs (such as markers with existing standards and harmonization, and basic biomarkers) or a single high-capacity facility (for certain selected platforms and markers, including both basic and exploratory biomarkers).
3. Each reference lab should participate in, and agree to, the following assay validation and delivery standards:
 - ▶ Adherence to key performance metrics (to be defined) including data quality management systems; development and provision of standardized IO assays using standardized protocols and methods; and banking, tracking, and distribution of biological samples in a compliant manner that would allow dissemination to clinical practice
 - ▶ Delivery of data in standardized formats, for example, in:
 - ▷ IHC: e.g., intensity scores, percent tumor cells at each intensity, H-score, special locations
 - ▷ Next Generation Sequencing (NGS): e.g., BAM files, VCFs
 - ▷ Other scoring methods/algorithms: e.g., immune cell infiltration patterns
 - ▶ Routine, regular performance reviews focused on quality, proficiency testing, and compliance

Value Proposition

The establishment of a network of reference labs will enhance the efficacy, quality, and power of biomarker analysis across immunotherapy trials. By applying standardized sample processing and assay protocols, deviation of test results due to pre-analytical and analytical variations will be minimized, allowing for cross-trial comparisons. Systematic incorporation of key biomarker modules will expand the power of individual trials through combined analysis with other trials.

Approximate Project Budget

The estimate costs for this project is based on the NCI budget for CIMACs, as well as the PACT basic biomarker cost estimates:

(b) (4)

The PACT funds raised to synergize with the CIMACs effort from NCI will:

- ▶ Cover the expenses of the PACT-initiated biomarker projects within PACT selected trials.
- ▶ Expand the testing services of the existing CIMAC network formed from NCI funding to establish assays for biomarker studies in trials prioritized by PACT.
- ▶ Add new assays or platforms to existing capacities.
- ▶ Add new labs with specialized capabilities of novel technologies or expand the general capabilities of the network.

Project 1.3 — Creating a database for all PACT biomarker data

Challenge/Opportunity

A pre-competitive common database or data access platform is particularly important for immunotherapy biomarkers, since individual trials, even large Phase III trials, may not have sufficient power for complex correlative analysis. However, there currently is no widely available repository that contains biomarker data for IO; instead multiple databases are being implemented without coordination and therefore without consistency. Because IO biomarker research is a nascent field, there is a huge opportunity to ensure early data harmonization

and standardization optimization. The definition, collection, storage, and sharing of data and metadata from multiple sources must be standardized: reproducibility of research results and the ability to broadly translate findings will be impossible without such standardization. The data types to be collected, and the adoption or creation of open standards for storing them need to be determined.

Solution

NCI and NIH already have programs to establish unified data repositories that enable data sharing across cancer genomic studies and that are made accessible to the scientific community, such as the Genomics Data Commons (GDC). Construction of both an Imaging Data Commons and a Proteomics Data Commons is also actively proceeding. An NCI Cancer Immunologic Data Commons (CIDC) is in the planning stages and is a natural extension of this concept, and the timing of this effort aligns well with the PACT initiative. Analysis will need to be performed to determine the appropriate model for such a repository, e.g., whether it makes more sense to create a single database to which contributors send their data, or to use a federated model, where researchers can access, combine, and analyze the data as it is acquired from multiple sources. Once a model is defined, collection mechanisms will be created to ensure the data are obtained in a fashion that does not require double or duplicative data entry. This resource will also need to have the capability to house or access corresponding patient level clinical data, i.e. diagnosis, key demographics, treatment history, and outcome history. This feature will be absolutely critical in order to make the resulting biomarker information truly useful.

Another key component for the PACT database will be that contribution of data will be mandatory for all NCI led trials; however, it is understood that for company-driven trials, participating may be limited by the presence of proprietary information. Company sponsors would therefore be allowed to limit the outcome data placed in the repository as necessary. A staged approach will be needed for implementation.

There are multiple NCI programs that have potential relevance to this Project 1.3:

- ▶ **NCI programs where large amounts of relevant data are being collected** already exist and can be leveraged for PACT.
- ▶ CTEP supported Clinical Trial Networks (as mentioned in Project 1.1). The NCI provides significant resources to the CTEP infrastructure. The NCTN grants a total of approximately \$150 million/year for trials, and the ETCTN grants a total of approximately \$20 million/year for trials. In addition, NCI also issues support contracts (CTSU, CIRB, etc.) for both total that total approximately \$60 million/year. In short, this means that during the first 5 years of PACT, the NCI will invest ~\$1.1 billion/5 years or ~\$230 million/year to conduct clinical trials. Many of these trials are currently studying IO agents or combinations with IO agents. Data generated from some CTEP trials may be used for standardization and harmonization and serve as the initial population of the CDIC.

- ▷ The Quantum Immuno-oncology Lifelong Trial (QUILT) is developing a Master Protocol, and the blanket consent can be adopted to allow the data generated to be broadly shared.
- ▷ The NCI Center of Excellence in Immunology's (CEI) mission is to foster discovery, development, and delivery of novel immunologic approaches for the prevention and treatment of cancer and cancer-associated viral diseases. The CEI collaborates with the CITN, partners with the Society for the Immunotherapy of Cancer (SITC), and fosters collaborations with Biotech and Pharma.
- ▶ **NCI and private sector efforts to develop platforms for immunological data deposition, integration and/or analysis will help guide the CDIC design efforts.**
 - ▷ NCI has an initiative to establish a CIDC (a U24 mechanism RFA is in the planning stages), which would serve as a bioinformatics core center for research data collection, analyses, integration, and data sharing for studies completed by the CIMACs. This effort can be leveraged as the starting point/prototype for the Immunological Data Commons as well as for the data generated by the CIMACs. The short-term goal for this project is to collect and integrate data to allow within- and cross-trial analyses for NCI network studies. The longer-term goal is to provide a common platform to make the data accessible by the IO community and to allow integration with data from outside the NCI. This platform could be used to create common analysis pipelines, as has been done in the GDC for genomic data.
 - ▷ Platforms already exist for various data types or data integration (within industry, nonprofits, data/diagnostic companies, and academia). One example is ImmPORT, The Immunology Database and Analysis Portal, a partnership between researchers at the University of California-San Francisco, Stanford University, the University of Buffalo, the Technion-Israel Institute of Technology, and Northrop Grumman. It is funded by NIAID. ImmPORT can serve as a model for data integration.

Potential synergies between other ongoing efforts and PACT can be used to enhance both programs.

- ▶ Public/private partnerships, which can be leveraged to gain momentum and agreement on issues including the development and use of data standards, data sharing agreements, and the actual sharing of data that is being generated.
 - ▷ Global Immunotherapy Coalition (GIC)
 - ▷ Parker Institute for Cancer Immunotherapy
 - ▷ Bloomberg-Kimmel Institute for Cancer Immunotherapy

- ▶ Complementary projects, where efforts can be made to integrate with varied types of data (genomic, clinical, proteomic, imaging) and to accelerate the discovery and the development of new treatments
 - ▷ NCI Genomic Data Commons & Cancer Genomics Cloud Pilots—focused on genomics data harmonization and accessibility and analysis
 - ▷ NCI Imaging Data Commons (early-stage planning)—focused on imaging data harmonization and accessibility
 - ▷ NCI Proteomics Data Commons (early-stage planning)—focused on proteomics data harmonization and accessibility
- ▶ Other agencies
 - ▷ FDA development of standards for submissions of immunological biomarker data and related documentation designed to support potential regulatory marketing authorization, if applicable
- ▶ Standards development organizations
 - ▷ Clinical Data Interchange Standards Consortium (CDISC), including possible use of Study Data Tabulation Model (SDTM)
 - ▷ NCI Metadata Thesaurus and Cancer Data Standards Repository (caDSR)
 - ▷ Biomedical Research Integrated Domain Group (BRIDG), which is part of ISO
- ▶ Clinical trials conducted by other networks and companies
 - ▷ External trials may not utilize the same assays and platform as PACT studies but would still be useful to include in the database if there was sufficient information about the biomarkers employed to determine analytical validity.
 - ▷ Bridging or compatibility studies would need to be conducted for these trials, and data harmonization would need to be done. These tasks have been accounted for in the budget for this project.

Focus of the Project

Project 1.3 will:

- ▶ Develop a database platform—a “data commons”—that includes both published and unpublished data, to enable data sharing.
 - ▷ Selection of a database technology will need to account for the inchoate nature of this work, providing flexibility and mechanisms to standardize, store, integrate, and interrogate new types of data that will be generated. Clinical, safety, and biomarker data should be contained or accessible through one source. As much as possible, data to be collected should be defined up-front, with the understanding new data types will follow.

- ▶ Identify or enhance data collection tools for the types of biomarker data collected from the basic and expansion biomarker modules defined in Project 1.1, while concurrently developing new tools and data collection standards that may be needed for certain data platforms.
 - ▷ The biomarker data platforms will likely include tumor genomics, T-cell receptor sequencing, RNA-seq and NanoString, IHC or multiplex IF, flow cytometry, cytokine panels, and functional analysis.
 - ▷ As available, additional patient-level data will be included in the database to be paired with the biomarker data, such as diagnosis (e.g. cancer site, histology, staging), patient demographics (e.g. age, gender, race), treatment (e.g. medications, start / stop dates), and outcome history (vital status, disease status, relevant ancillary medications).
- ▶ Provide or develop tools to access and analyze the data and mechanisms to inform clinicians and basic and translational researchers of the challenges of drug combinations and how to optimize treatment for patients.
- ▶ Identify software to support data collection from participating institutions and integration of that data into the data commons.
 - ▷ Role-based security that takes into account HIPAA and FISMA requirements and a variety of authorization models must be an integral part of the system.
- ▶ Identify barriers to data sharing/transparency amongst various drug development parties and develop strategies to overcome those barriers.

Value Proposition

The goal of this project is to create a means to collate, maintain, harmonize, share, and curate the IO data collected in PACT-participating clinical trials, as well as any basic and translational research data that the PACT initiative may identify and request to be contributed to the database, such as that from PACT Program Area 2. The Cancer Moonshot Blue Ribbon panel has specifically called for a “national infrastructure” as a core component of the CITN, and that success will be measured by new, effective treatments “in more patients, across many different cancers.” Achieving this goal requires the ability to integrate and analyze multiple data types from a wide variety of sources. In addition to providing an IO biomarker database for the initial set of clinical trials, the ultimate goal of the repository is to provide access to the research community and enable analyses of the complex systems biology data, which will drive the more systematic and data driven selection of IO combination therapies. This will allow for more efficient drug trials to be conducted by companies and hopefully eliminate duplicative efforts across the field.

Approximate Project Budget

The estimated budget for this Project is based on the NCI Cancer Genomics Cloud Pilot costs and assumes we will be building upon existing resources.

(b) (4)

(b) (4)

1. \$10 million—Acquire storage and compute resources for database platform. Analysis needs to be performed to determine if in-house or cloud-based infrastructure is most appropriate. Security, Authentication, and Authorization components will be developed. Ongoing operations, maintenance, licensing, and leasing costs are included.
2. \$4 million—Develop a database platform, or “data commons,” that includes both published and unpublished data to enable data sharing. PACT will identify the appropriate data model, leveraging existing resources (e.g., NCI Thesaurus) wherever possible and work with community experts to define appropriate data models where standards do not already exist.
3. \$2 million—Identify or enhance data collection tools for the types of biomarker data prioritized to be collected from the basic and exploratory biomarkers defined in Project 1.1, while concurrently developing new tools and data collection standards for certain platforms. This will require establishment of data standards where they do not currently exist and will dovetail with Item 2 above.
4. \$2 million—Develop software/mechanisms to support data submission by participating institutions and integration, validation, and QA of that data in the CIDC.
5. \$2 million—Identify or develop tools to access and analyze the data and mechanisms to enable clinicians and basic and translational researchers to understand the promise and challenges of specific drug combinations and how to optimize treatment for patients. The PACT team understands that this amount will likely not be enough to fully develop all the tools necessary for these endeavors; however, the \$2 million will kick-start the development/enhancement of tools, which could also additionally be funded by grant programs such as Informatics Technology for Cancer Research (ITCR), as well as by private interests. In addition, it is recognized that having a critical mass of data available will be a catalyst for the community to start using it and improving upon existing tools.

This would supplement the \$1 million/year in the CIDC RFA for a total of \$30 million/5 years for both public and private sector funding.

Project 1.4—Assay standardization and validation for high priority basic biomarkers

Challenge/Opportunity

Biomarkers to improve the efficacy of immunotherapy for cancer patients are important tools in clinical management and drug development. Comprehensive profiling of the tumor immune interface with multiparametric technologies that encompass the dimensionality and complexity of the interaction of the tumor and the immune system is needed to monitor and stratify cancer patients for individual therapeutic requirements. A number of candidate biomarkers and platforms with the potential to be developed into assays to predict response to immunotherapy or monitoring have been identified in Project 1.1. The analyses are typically accomplished

through various laboratory assays to measure differences in specific tumor and immune parameters before, during, and after treatment. This may allow the identification of tumor and immune signatures, which correlate with immunotherapy response or resistance or immune related adverse events, and select patients for treatments using the biomarkers, including those identified in Project 1.1.

The diversity of reagents and approaches used in current IO research has produced a large variety of methodologies that are being used to assess the immune systems of humans and data reporting procedures that are frequently not consistent. This situation often hampers data reproducibility among laboratories, which hampers meaningful interpretation of results across studies and could lead to selection of different intent to treat populations. In addition, most of the assays used involve high-throughput multi-parametric “signatures” that require considerable statistical and bioinformatic efforts for proper algorithm development and robust data interpretation. Such capabilities are not currently available to all investigators assaying immune biomarkers and, therefore, biomarker testing is not consistently or uniformly being performed in academic or clinical laboratories due to resource constraints. Furthermore, there is no existing system that can easily integrate analyses across different clinical trials. Given these challenges, which others in the IO field have further detailed (van der Burg et al., 2011), assay standardization will be a critical focus of the PACT effort.

Different approaches to overcome these limitations and to address different technical and logistical challenges have evolved in the process of standardizing biomarkers. The importance of using standard guidelines for both specimen acquisition and analytical methods for biomarker measurements is widely recognized. First, biomarker measurements in clinical trial specimens should use high-quality, fully specified and validated assays. Second, the assay results should be comparable among clinical sites within a trial and between different trials. These goals may be achieved through use of central labs, assay standardization, harmonization, or concordance testing:

- The creation of validated assays with the kind of consistent pre-analytical, analytical, and post-analytical processes required for inclusion into clinical trials can be achieved through the **use of central laboratories** and a centralized biospecimen repository. A central laboratory that is affiliated with the entity sponsoring the trial offers the potential advantages of using the same validated assay to screen all patients and ensuring responsiveness and familiarity with the clinical trial. In addition, flexible, close communication between clinical and research teams during assay validation can be important elements for success in making a biomarker assay viable for use across different studies. Centralized testing provides assurance about the performance of a test, and minimizes differences in test performance or result reporting that can confound the definition of the intent-to-treat population within and across clinical trials. The ability to offer testing at central laboratories allows for integrated testing, sample management, and data-management services, which can facilitate efficient and reliable biomarker testing and data delivery as part of the comprehensive biomarker characterization.

- ▶ An alternative approach that facilitates the comparability and integration of data across multiple laboratories is **assay standardization**. Assay standardization and traceability to reference materials insure the most accurate and meaningful test results. Standardization also makes interpreting laboratory results easier for the physicians providing patient care. Because each assay can have its own reference interval, physicians currently must be able to apply the same reference interval to each test performed by a specific laboratory in order to accurately interpret that laboratory's results and to be able to compare across laboratories. With standardization, analytical results are more likely to be similar across all testing methods so that only one reference interval is needed, significantly decreasing the burden currently placed on physicians in interpreting laboratory results. Standardization is not a one-size-fits-all proposition. It requires development of standard unit measurement definitions, consistent calibration points, and standardized primary and secondary reference methods and/or materials for each analyte.
- ▶ Since reference materials and standards do not exist for many protein and nucleic acid analytes, **harmonization of biomarker assays** is another approach. Harmonization allows for the establishment of assay-specific protocols in individual laboratories while minimizing differences in assay performance due to assay-related variables. The use of identical reagents, instrument platforms and/or protocols and scoring criteria across laboratories is one solution, but this may not be feasible across many different laboratories. The harmonization process involves the participation of multiple laboratories in a consortium-based iterative testing process to identify the variables crucial for assay performance. To begin, individual laboratories participate to perform parallel quality control experiments on replicate samples with assay proficiency panels using the labs' own reagents, instrumentation, and protocols. A central laboratory manages logistics for the proficiency panel, receives raw and analyzed data sets from each participating laboratory, and provides independent central data analysis. During initial proficiency panels, variables are identified that impact test performance across the labs. Subsequent independent panels are then used to optimize protocols and harmonize the assay-related variables across laboratories (van der Burg et al., 2011).
- ▶ An example of an effort that addressed **concordance testing** or a comparability approach across multiple IHC-based PD-L1 tests was the Blueprint PD-L1 IHC Assay Comparison Project, which is a collaboration between the International Association for the Study of Lung Cancer, American Association of Cancer Researchers (AACR), four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech/Roche), and two diagnostic companies (Dako/Agilent and Ventana/Roche). Further detail and other examples of harmonization projects are in **Appendix 2**.

Solution

A part of methodological improvements for tumor and immunoprofiling assays provided in PACT will involve the creation of validation guidelines for immunoassays to support immune biomarker application and development for clinical trials. Part this project will enable the standardization and validation of assays to interrogate the IO biomarkers identified in Project 1.3. Standardization

and validation of the assays to be used for multisite trials and across different trials should minimize variability in assay results and provide an opportunity for comparability across sites and studies. Achieving a high level of data reproducibility and data comparability will help to accelerate the development of therapeutics targeted to specific biomarker-selected patient populations.

Focus of the Project

This project will likely have two aspects: 1) assay standardization/harmonization and 2) establishment and distribution of standard operating procedures (SOPs) and best practices.

1. Assay standardization/harmonization

First, 1–2 core laboratories from within the core laboratory network will be selected to validate existing assays for the PACT basic biomarkers. These laboratories should be able to establish technically and analytically validated assays that include several continuous steps of biomarker development. Technical and analytical validation refers strictly to the performance of the assay. Assay clinical validation occurs as part of the outcome analysis in clinical trials that ensures that the assay performs robustly according to predefined specifications (fit-for-purpose) that will establish acceptable criteria for use in future studies. Clinical utility, which refers to establishing the use of a biomarker test leads to a favorable benefit-to-risk balance, that is, guides clinical decisions that lead to better outcome, should also be planned.

PACT projects can be tasked to address various aspects of assay validation and standardization for selected markers based on the PACT JSC recommendation:

- **Evaluation of pre-analytic factors:** An important step in biomarker validation is the evaluation of **pre-analytical factors** that may affect assay performance due to specimen-related variability. For immunotherapies, for example, there may be a need to monitor *ex vivo* immune responses in phenotypical or functional assays, which require high-quality samples to ensure reliable analytic output. To ensure that optimal pre-analytic processing regimens are followed, SOPs for controlling specific biomarker development steps are essential. In general, best practice metrics can be defined for various parameters depending on the specimen type to be used. For instance, protocols for blood collection and processing, tumor collection, sample fixation and processing, and storage media optimization are often developed. To improve standardization of specimens, NCI has published best practice guidelines for biospecimen collections (National Cancer Institute, 2011). PACT will endeavor to follow these published guidelines where possible and make modifications where needed. Additionally, pre-analytical considerations for certain assay types can be found in **Appendix 2**.
- **Technical and analytical validation:** Analytical validation involves establishing the performance of an assay for its intended biomarker measurement. Analytical validation studies can include 1) accuracy, 2) precision, 3) analytical sensitivity, (4) analytical specificity, 5) reportable range of test results for the test system, 6) reference intervals (normal values) with controls and calibrators, 7) intersite reproducibility if the assay is to be performed in multiple laboratories, and 8) establishment of appropriate quality control measures (Becker,

2015; Jennings, Van Deerlin, Gulley, & College of American Pathologists Molecular Pathology Resource Committee, 2009; Landis & Koch, 1977; Linnet & Boyd, 2012; Mandrekar & Sargent, 2009). There are also validation study considerations depending on the type of assay and specimens that are used. For example, reader precision studies are needed for IHC tests, whereas molecular assays require accuracy studies. Whether the assays are for integral, integrated, or exploratory biomarkers, they must be fit-for-purpose and meet the acceptable criteria defined for the intended use in patients and trials. PACT will be able to use samples from trials that participate to perform technical validation of assays, when deemed necessary and approved by the trial sponsored.

- **Clinical validation:** After an assay has been analytically validated, PACT-associated laboratories may also be able to carry out **clinical validation** of the assays to determine whether the assay result has a clinically meaningful correlation with the condition of interest—for example, whether the assay reliably divides the patient population(s) of interest into distinct groups with divergent expected outcomes to a specific treatment. The laboratories will be asked to perform assays for integral biomarkers (for treatment eligibility) in a CLIA-compliant laboratory, and use of the test in a trial may need to be performed under an IDE from the FDA if it is a significant risk trial. This aspect will not be a requirement of all PACT-associated laboratories.
- **Assay harmonization and concordance testing:** For certain biomarkers and assay platforms, there may be a need for assay harmonization between labs or testing of concordance between validated assays. Such projects will be prioritized by the PACT Joint Steering Committee depending on the scientific importance or the clinical trial needs of PACT to have these assays become part of the basic biomarker modules and uniformly performed across all PACT-associated trials.

2. Establishment and distribution of SOPs and best practices.

The PACT core laboratory network group will create a **committee** to coordinate efforts and to promote synergistic research efforts among the core laboratories. This Core Laboratory Committee (CLC) will meet monthly and review to progress in developing biomarker assays and report its findings to the PACT JSC. It would operate as a work group of the JSC, but would remain a separate entity reporting to controlled by the NCI CIMACs. The CLC will select best practices from the CIMACs and generate and distribute SOPs and other materials among the core laboratories to keep the assays standardized and updated with best practices. These SOPs and materials will be shared with external partners that wish to run the PACT modules in their trials and contribute their data, but not use the PACT core laboratory network.

Evaluation and prioritization of biomarkers and platforms for which validation will be required will be assessed by the PACT JSC.

Value Proposition

The biological complexity of the tumor and immune system interaction poses multiple challenges associated with technical development of clinically applicable assays when evaluating different variables as markers of clinical benefit to immunotherapy. However, each of the potential biomarkers and their associated assays requires high-quality validation in order to be used effectively in clinical applications. Considering the increased relevance and emphasis on biomarker development in cancer immunotherapy, there is an enormous need to facilitate and improve the steps to demonstrate clinical value of molecular diagnostics in this space. PACT will apply standardized approaches for biomarker validation described above, when necessary, to enable more efficient assay development to identify IO-relevant biomarkers, which are crucial to guide personalized therapy and for advancing IO options for cancer patients.

Approximate Project Budget

The cost of this project will be tied to the time and resources necessary to establish an analytical performance of each assay. Because flow cytometry, IHC, DNA/RNA sequencing, and other analytical methods constitute a large segment of the molecular characterization of the tumor and immune profiling, they will likely be the first validated for specific use. The estimated cost for running each assay for validation is \$500–\$1,000/sample, depending on the assay type (~\$500/sample for IHC versus ~\$1,000 for some flow cytometry panels), with the likely need to perform comprehensive analysis of 100 samples to validate any assay head-to-head. Cost for one assay comparison would then be ~\$50,000–\$100,000. For more complex assays, there could be additional costs even beyond this estimation. There would also be additional costs associated with time of the technical staff, biostatistical staff, and computer scientists for stand-up of the assays within the labs and the postanalytical phase of assay validation. The hope is that these costs could be partially defrayed since the CIMACs will already be established. In addition, PACT would hope that the cost for the samples for these validation assays would also be low due to the availability of banked samples in the PACT biorepository.

Project management and organizational support for the panel and team will also be required in order to assemble and keep current the materials for the drafting and review of the SOPs. A small team to do this—contracted separately from the core laboratory network and including one project manager and one science writer at full-time salary and benefits, plus the meetings and supplies—would cost ~\$400,000/year.

The following table summarizes the total budget for Program Area 1:

Program Area 1 Consolidated Budget

PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)	TOTAL PROJECT COST
Project 1.1.1 and 1.2	Create core laboratory network to conduct biomarker assays	(b) (4)	(b) (4)
Project 1.1.2	Develop new IO biomarkers		
Project 1.1 and 1.4	Expand biorepository capabilities for sample storage		
Project 1.3	Create database to bank IO biomarker data from clinical trial		
Project 1.4	Standardize and harmonize biomarker assays for IO therapy		
PROGRAM AREA 1			\$205.75M
Program Area 1 — “Buy-up” Option ► Supplement to defray costs of additional tissue collection at clinical sites			

Program Area 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners

Project 2.1 – Landscape analysis and literature review of biomarkers being developed and IO and other therapy combinations being tested across the oncology field

Challenge/Opportunity

One of the primary hurdles the PACT initiative will face is that the field of IO is moving at such a rapid pace compared even with other portions of the cancer research and clinical fields. This accelerated pace of research, drug development, drug release, and clinical use of IO therapies will make it challenging for PACT to select which biomarkers to develop and test unless these deliberations are accompanied by a “real time” effort to gather information on all of the current trials and related activities in the field. Specifically, the Scientific Project Selection Panel (SP²) and Joint Steering Committee (JSC) will need guidance on which biomarkers and combination therapies are being tested or are in development. A crucial piece to development of this guidance will be to produce it quickly as the timeline will need to parallel the IO drug development pace.

Solution

To stay current and synergize most effectively with other efforts in the IO and oncology field, we propose to have a small team of science researchers and writers regularly conduct a landscape analysis of critical efforts in the IO field. The first fully comprehensive landscape analysis will occur just after the launch of the PACT initiative. This comprehensive analysis will likely take approximately 1–3 months to fully research all publically available information about ongoing biomarker and combination trials within the IO space that have taken place to date, and then compile that data into a digestible format for the SP² for review. This group will also engage with PACT company members to acquire data on the emerging company trials, as well as to gain any organizational insight into the IO landscape that can assist in the selection of combination therapies and biomarkers to be addressed through PACT.

The landscape analyses will include publically available data from publications, websites (e.g., clinicaltrials.gov and others), abstracts, and corporate websites and publications, as well as insights gleaned directly from conversations with relevant industry representatives, both PACT and non-PACT members as appropriate. Both public and private information will be collected, and the FNIH (or its contractor) will act as a neutral third party to collect the data. Two versions of a summarized report will be generated: 1) a high-level summary devoid of any proprietary data, which can be reviewed by the entire PACT JSC to assist in decisions, and 2) a more detailed summary which may include some proprietary data—as necessary and if willing to be shared—to be reviewed only by the SP² (which, it should be recalled, will include no members of competing pharmaceutical companies, but only academics and ex-company members with no conflicts of interest). The authors of the landscape analysis as well as the SP² members will be bound by confidentiality agreements.

From this analysis, the team will create and maintain an up-to-date summary clinical trial compendium for combination therapies and biomarkers in development from current and emerging data across the entire IO space enabling categorization of trials into three types: 1) highly relevant to the entire IO field, funded trials; 2) proposed trials that are highly relevant to the IO field but currently unfunded; and 3) trials of low relevance. The SP² will review this compendium and use it to make recommendations to the JSC about which trials and resulting biomarker modules PACT should pursue, and which trials PACT should help to co-fund. As a secondary feature, the SP² will also be able to make recommendations to the IO outreach team about which groups to work with to develop cross-fertilization efforts and which other groups to approach about depositing their trial data into the PACT database for harmonization with PACT biomarker modules.

After this initial landscape analysis is generated, it will be shared with the appropriate governing bodies for PACT to allow them to make their initial decisions. A landscape update will be conducted biannually each year the PACT initiative continues. These biannual updates will take place in the month immediately following the annual meeting for the American Society of Clinical Oncology (ASCO) and the European Society for Molecular Oncology, which usually occur in early summer and late fall. These meetings usually have the largest release of data from all stakeholder groups relevant to the PACT initiative and therefore will be ideal targets for the landscape updates. While these meetings will be the primary target for data review due to the large amounts of new data released, the analysis will also be sure to account for data released at other meetings in the time between landscape scans, such as the ASCO, American Society of Hematology, American Association of Cancer Research annual meeting, and others. After each update, a report similar to that generated after the initial landscape analysis will be prepared and shared with appropriate committees.

Value Proposition

A full picture of current and upcoming biomarker testing will allow the PACT teams to continuously update its pipeline of basic and exploratory biomarker modules. Having the most current list of IO combinations being tested will also allow the PACT initiative to approach

the right individuals with whom to discuss incorporating their markers and trials into PACT, and help construct a knowledge base to help guide the field with respect to choosing future combination studies.

The landscape analysis will also help support the active outreach to other groups that are working in the IO space described as part of Project 2.2.

Approximate Project Budget

(b) (4)

The total cost for this project is therefore estimated at ~\$1 million dollars over the 5 years.

Project 2.2 – Selection of trials with high-priority combination therapies and biomarkers for co-funding by PACT

Challenge/Opportunity

As mentioned above, PACT will not establish its own clinical trials network infrastructure or fully sponsor and conduct the trials itself (i.e., contract with selected clinical sites; finance and monitor patient accruals; hold INDs; conduct safety reporting; submit registrations etc.), but will work with existing trial networks to implement clinical trials that will use the PACT biomarker modules. These clinical trials may come from the NCI's clinical trial networks (e.g., ETCTN, NCTN, CITN, and COG), industry, academic investigator-initiated trials, or nonprofit consortia (e.g., Stand Up 2 Cancer, Parker Foundation IO Consortium), provided groups are willing to work with PACT and implement the biomarker modules within them. Partner trials will be selected by the PACT JSC based on the landscape analysis described in Project 2.1 after review by and based on the recommendations of the SP². JSC will next work with an outreach project team from FNIH to help broker a partnership for PACT biomarkers on those trials and eventual deposition of the data into the common database. This outreach project team could also encourage companies or other trial networks to initiate new trials using some of the high-priority combinations identified by the SP² if these trials are not currently in the pipeline. (This is further described in the description of Project 2.3 below.) The PACT team also recognizes there will be a few particularly high-value combination trials to be conducted that need some supplemental funding in order to be launched, as they may not be within the short-term pipeline of any company. PACT will work

to facilitate partnerships between the necessary companies to initiate these trials, PACT can consider providing supplementary funding to conduct these trials through mechanisms already available, or it may choose to institute a unique RFA mechanism for these trials.

The following are some examples of how this will work:

- ▶ **Example 1: PACT initiates new trials for novel combinations and supports the relevant biomarker studies:** A new high-priority treatment or combination regimen is identified by the SP², and the JSC decides it should be a PACT trial because the biomarker and clinical objectives would fill critical gaps in the field. However, the companies with the compounds of interest are not able to prioritize their resources to fund the clinical and biomarker studies in their entirety. (Or, alternatively, PACT proposes new trials for combinations already in clinical testing, but finds that additional studies with alternate designs or clinical settings are needed (e.g. with pharmacodynamic endpoints or biomarker stratifications) to address critical biomarker or clinical questions not otherwise tested.) In this case, PACT approaches the companies and offers to help support the costs of the biomarker testing. The size of the trials may range from small phase I/pilot studies to larger phase II trials. As an example, one could estimate a trial of 50 patients to cost ~\$6 million. PACT could invest ~\$2 million to conduct the biomarker assays and some site supplements. If the trial were to be conducted through the CTEP infrastructure, CTEP would supplement payments to trial sites to cover ~\$2 million. This would then leave the companies with only ~\$2 million to raise to conduct the trial. It is the hope that this reduced cost would incentivize the companies to participate in the trial as part of PACT.
- ▶ **Example 2: PACT supports biomarker studies in ongoing/planned trials:** The SP² identifies an existing clinical trial involving immunotherapies that are suitable for high-priority biomarker studies, and the JSC decides it would fit well as a PACT trial. However, the companies sponsoring the trial are only able to conduct limited biomarker assays. In this case, the PACT team will approach the sponsoring companies (or clinical trial network, depending on the trial structure) and ask them to collect samples to run at least the basic biomarker modules in their trial. In this case, PACT pays for the testing of these biomarkers only. If one assumes this is a phase I/II trial with a cohort of 50 patients, then the PACT supplement for this trial would consist of \$500,000 to conduct the biomarkers plus an additional \$500,000 to supplement collection and storage of the additional samples needed for the biomarker testing. This would result in a total of an approximately \$1 million trial supplement. Trials of this type could come from either the NCI Clinical Trials Networks or from the private sector.
- ▶ **Example 3: PACT supports biomarker studies in completed trials:** The SP² identifies a clinical trial of a high-priority therapy combination or biomarker objectives that has already been conducted and for which properly banked biospecimens are available, and the JSC decides it would fit well as a PACT trial. PACT funds the conduct of basic biomarker modules on the samples. (This may be phase I, II, or III trials.) The cost to run the basic biomarker modules would be tied to the number of patient samples. If the trial collected 200 patient samples, the cost would be ~\$2 million to run the basic biomarker assays.

As noted in each of the examples, once drug combinations of interest or existing clinical trials are identified and the decision to provide PACT support has been made, the PACT outreach team from Project 2.3 will work to recruit the necessary partners. In addition, as the PACT program develops, a mechanism can be established for teams to send proposals for priority combination therapy trials to the JSC for review independent of the landscape analysis.

Value Proposition

Co-funding trials through PACT will enable trials that would not normally be conducted by companies on their own, but that have high potential value to the field, to be conducted, with the resulting data shared with the research community. Co-funding could also be a means to conduct retrospective biomarker assays on banked samples from high-priority data that would substantially add to our understanding of the science behind IO and related combinations.

Approximate Project Budget

Costs for this project will be partially accounted for in the biomarker budget for Project 1.1, as one of the main aspects of co-funding will be to pay for testing of the biomarkers for the trials. However, it is anticipated that there will also be a need for funding for an RFA to support 5–10 of the highest-priority trials to be conducted during the first 5 years of PACT. It may also be possible to create an RFA for clinical trials through either the ETCTN or NCTN. (b) (4)

(b) (4)
(b) (4) Co-funding could range from simple biomarker support to partial trial funding. The RFA could be administered either through FNIH or NCI depending on the desired needs and structure of the partnership.

Further PACT Trial Co-Funding (Optional)

The amount for co-funding detailed here represents an initial investment by PACT to assist in getting important trials conducted. (b) (4)

(b) (4)
(b) (4) This further funding can be determined in future years and on a trial-by-trial basis with the funding partners if the PACT model proves to be successful.

Project 2.3 – Active outreach and coordination with other ongoing IO/oncology efforts

Challenge/Opportunity

As a logical counterpart of its biomarker development, assay standardization, data integration, and trial (co-)funding mission, PACT is designed to serve as a clearinghouse and coordination point for information and insights on potential IO and combination therapy research. Given this PACT will need to coordinate actively with the many existing and emerging public and private research efforts in the field.

Solution

A scientific program management team at FNIH and experienced in facilitating the work of public- private partnerships will leverage the information from the landscape analyses that are ongoing in Project 2.1 to conduct targeted outreach and establish external collaborations with similar programs supported by biopharmaceutical companies, nonprofits, academic medical institutions and government agencies. This team will work to coordinate efforts continuously across all active IO efforts, avoid duplication, share information, and ultimately meet the PACT objective of a systematic translation, evaluation and validation of biomarkers and assays.

Value Proposition

A proactive, constant outreach to and involvement of other IO/combination efforts will allow the most efficient use of the investments of PACT stakeholders and there sources available in the field, given biological complexity of immunotherapies and related combinations and the breadth and depth of what must be learned in order to deliver effective treatments to patients.

Approximate Project Budget

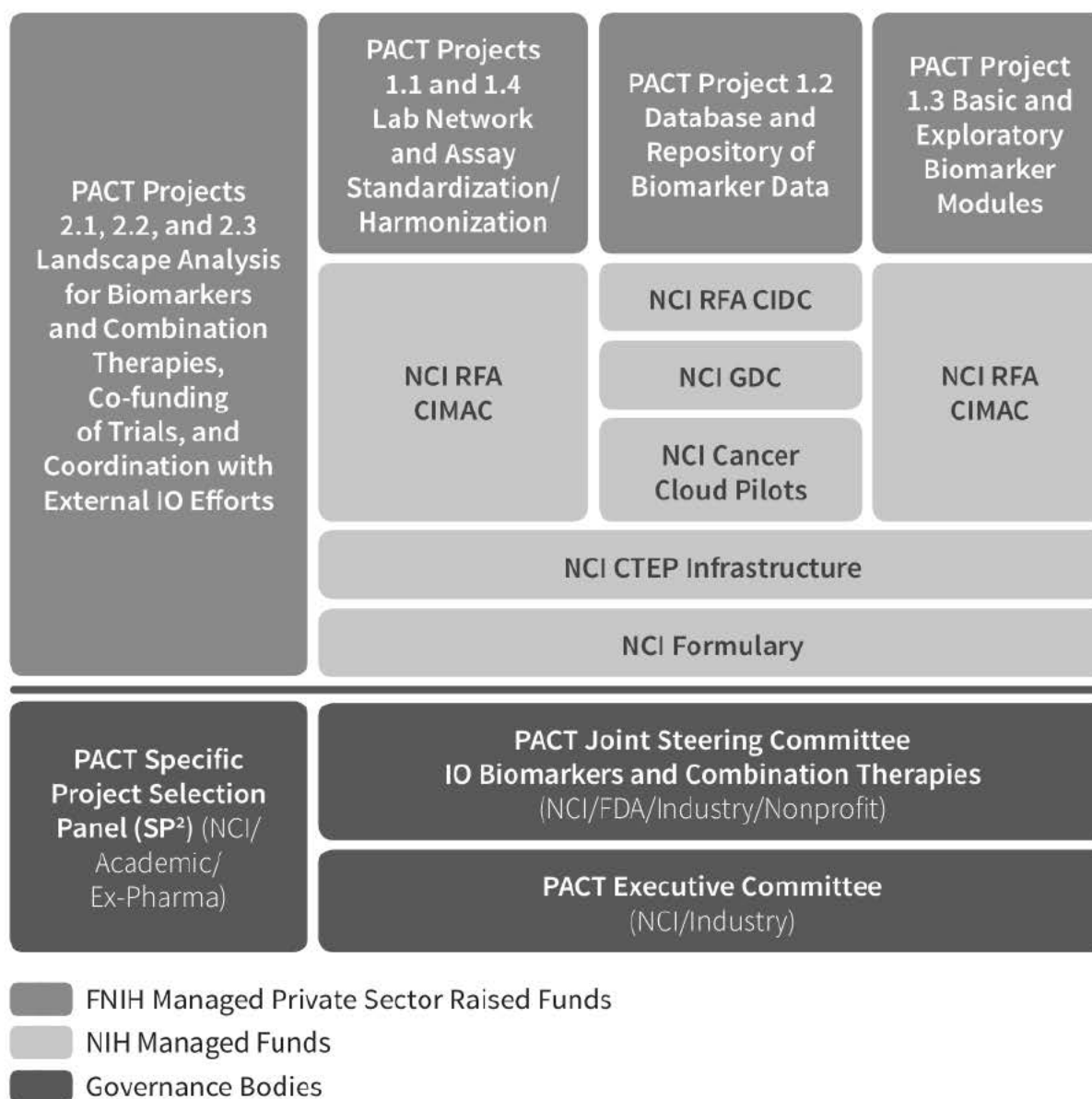
(b) (4)

The following summarizes the total costs to support Program Area 2:

Program Area 2 Consolidated Budget

PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)	TOTAL PROJECT COST
Project 2.1	Conduct biannual landscape analysis to determine priority biomarkers and combination therapies	(b) (4)	(b) (4)
	Compensate SP ² members for trial and biomarker landscape review		
Project 2.2	Co-fund high-priority combination clinical trials		
Project 2.3	Conduct outreach and coordinate with other IO efforts		
PROGRAM AREA 2			\$28.65M
Further PACT Trial Co-Funding (Optional) ► Additional funding for specific clinical trials and biomarkers, which can be decided on a trial-by-trial basis			

PACT Governance



To achieve its objectives, PACT will require a governance structure that 1) maintains close involvement by both public and private partners in key decisions; 2) protects confidential or proprietary information and guards against conflicts of interest; 3) provides both continuous strategic direction for the partnership and rigorous operational management of its different component parts; and 4) enables timely decision-making, avoiding unnecessary bureaucracy. To accomplish these goals, we propose four **focused governing bodies to run the partnership**:

1. An operationally focused PACT Joint Steering Committee (JSC), each member of which will direct different aspects of the PACT research plan.

2. A PACT Scientific Project Selection Panel (SP²) to analyze existing and potential therapeutic and biomarker studies and make recommendations regarding which biomarker studies could be executed as part of PACT. This will be an advisory rather than decision-making body. The JSC will make the actual selection of which trials should be part of PACT based on the SP²'s recommendations.
3. A PACT Executive Committee (EC) to provide high-level strategic direction, communication with the top leadership of each of the partner organizations, and resolution of general policy issues. The EC will oversee the actions of the JSC and the SP² and communicate with other PACT partners via an Extended Executive Group, consisting of senior executives from partner organizations not actively serving on the EC.
4. In addition, a PACT Patient Advisory Committee (PAC) will be added to the governance structure of PACT upon the launch of PACT years 4-5, consisting of representatives from cancer patient advocacy organizations. The PAC will periodically review the progress of PACT and provide input to the EC and JSC on PACT's relevance to and support of cancer patient needs and concerns.

PACT Joint Steering Committee (JSC)

Execution of the research programs in PACT will be governed through a JSC composed of members from participating companies, government agencies, and nonprofit organizations. The JSC will operate under the direction of the PACT Executive Committee (EC).

The responsibilities of the JSC will include:

1. Reviewing the recommendations of the PACT SP² (described below) and using these recommendations to set operational research priorities for PACT programs, including selecting the optimal combination therapy trials for PACT partnerships.
2. Reviewing the progress of projects on an ongoing basis and adjusting project plans to ensure appropriate tradeoffs between the timely achievement of key project milestones and production of quality results. The JSC is therefore the primary forum for discussion among the PACT partners of potential operational changes to the final research plan, based on emerging opportunities and challenges, and within the context of the project budgets.
3. Meeting regularly with the Core Laboratory Committee (CLC) to ensure lab coordination and development and distribution of SOPs and best practices.
4. Conducting assessments of key project milestones, including critical go/no-go milestones, and communicating these assessments to the EC.
5. Determining how private sector funds provided to FNIH are distributed (consistent with the final research plan).
6. Working with the potential PACT PAC, which will be composed of patient advocates.

7. Reviewing the results of the research efforts under PACT and making recommendations regarding how they are disseminated and publicized, consistent with NIH publication rules.
8. Overseeing active outreach to, and coordination with, other related cancer research and trial efforts as described in Project 2.3 (above).

While the final overall research plan for PACT will be decided jointly by NIH/NCI and industry partners, the funds provided by NIH and industry for PACT will flow through separate streams. NIH funds must be disbursed according to NIH procedures for solicitation of applications, review of applications, and decision-making. NIH will have final statutory decision-making authority over the conduct of its grants, as provided in the federal regulations, although private sector partners will have the ability to provide input on the progress of the NIH-funded research through the JSC.

Private sector partner funds will be contributed through and managed by FNIH. (FNIH will also coordinate any material in-kind private sector contributions to PACT.) Such funds may be dispersed directly by FNIH through grants or contracts, or transferred by FNIH to NIH for disbursement through NIH grants. The JSC will review and select proposals made directly to FNIH for funding. After awards are made, the JSC will provide project oversight for all studies, whether funded by NIH or industry/FNIH, in a manner consistent with NIH procedures as described above.

The membership of each of the JSC will be as follows:

- ▶ Three to four NIH members (voting), including program officials for the relevant NIH grants
- ▶ At least one representative from FDA (nonvoting)
- ▶ One voting representative from each funding industry partner; additional industry representatives may attend as alternates but will be nonvoting
- ▶ One voting representative from each nonprofit organization that matches company funding levels for PACT
- ▶ Subject matter experts, such as academic investigators, whether funded by PACT or not; may be added at the JSC's discretion, but will be nonvoting
- ▶ At least one representative from FNIH (ex-officio, nonvoting)

The JSC will be co-chaired by one NIH and one industry representative, selected by the PACT EC, but who is not part of the EC.

After the projects are launched, the JSC will meet regularly (likely monthly) via teleconference, and at least twice yearly in person. The frequency of meetings will be adjusted as the scientific agenda requires. The JSC may also convene smaller “working groups” of experts that include PACT stakeholders to advise on specific areas of science or technical aspects of the research plan. The decisions of the JSC will be made by simple majority. Each participating company will have one vote as will each qualifying nonprofit partner, and the resulting private sector cumulative

vote will remain constant at 50 percent of the total votes. If additional industry members are added to the partnership, votes for all industry participants will be scaled appropriately. NIH will have votes that will not exceed 50 percent of the total. The goal of the JSC will be to drive consensus on partnership decisions. In the unlikely event that this cannot be achieved, any conflicts will be raised to the EC for resolution. JSC operational logistics, staffing, and project management will be managed by FNIH.

PACT Scientific Project Selection Panel (SP²)

Some of the most important decisions made in the course of PACT involve choosing appropriate studies or projects to execute using the PACT infrastructure or with PACT funding. These include consideration of which biomarkers or preclinical models to develop, around which drugs or drug combinations these efforts should be focused, and—for Program Area 1 (biomarkers)—which clinical trials should be selected to have biomarker studies executed in PACT (Program Area 2). We expect that proposals to execute combination clinical trials with biomarker studies defined in the modules within PACT will be of several different types:

1. A proposal for a biomarker “companion study” to be run using an NCI-sponsored (ETCTN or NCTN) trial as a “backbone,” where samples and clinical data collected from such trials are run through the PACT infrastructure.
2. A proposal to test combinations brought to PACT by one or more industry partners, where samples and data collected from these trials would be developed using the PACT core labs.
3. External sponsors of individual trials could also choose to run PACT biomarker modules using PACT-developed assays and standard SOPs in labs they select outside the PACT core labs and contribute data back to the NCI Data Commons.

Evaluating studies that are proposed to run under PACT or which datasets to accept into PACT will require significant scientific expertise, potential access to sensitive or confidential company data (such as proposed trial protocols, results of point of care or early-phase preclinical or clinical studies, investigator brochures), and the ability to provide objective recommendations that are based on the science rather than individual commercial considerations. In this regard, the JSC will need to rely on advice from a separate panel of oncology experts who are knowledgeable about oncology (with a particular focus on IO) and who have practical experience in biomarker and therapeutic development, but can provide objective advice and are free of conflicts of interest with regard to the interests of specific companies. PACT will establish the SP² to fill this advisory role.

The SP² will determine which potential therapeutic combinations and which biomarkers have the highest priority for assessment in the PACT infrastructure. The SP² will oversee the conduct and distribution of the landscape analysis described in Project 2.1 above and will use information from the landscape analysis and other sources to identify candidate studies for PACT. FNIH will provide research services (through a subcontracted consulting group if needed) to collect

the background information needed to assess these studies. FNIH (or its subcontractor) will execute the necessary confidentiality agreements with companies and other entities whose studies are being considered by the SP² and with individual SP² members to ensure proprietary or confidential information is used only to support PACT decisions and is protected from inappropriate disclosure. The SP² will focus on combinations that address currently unmet needs for the field and for patients (i.e., are not effectively being tested elsewhere) and that offer a compelling scientific rationale for inclusion in PACT and make specific recommendations to the JSC about which studies to pursue. The SP² may also communicate its most general findings more broadly where they may be of use to specific sponsors or to the oncology community.

The membership of the SP² should include the following:

- ▶ NCI scientists and medical officers with expertise in PACT interest areas. This may include one or more members of the JSC who can act as liaisons.
- ▶ FDA scientists.
- ▶ Academic researchers with relevant clinical and translational research expertise. These members, while they serve on the panel, will not be able to serve as principal investigators on studies associated with PACT.
- ▶ Scientists with industry experience in oncology drug development who do not have current employment with or active ties to individual companies in the areas of interest for PACT, to avoid conflicts of interest.
- ▶ One or more representatives from nonprofit/patient organizations with an interest in IO.

The SP² will meet at least quarterly (or more often if needed) by teleconference. Two of these quarterly meetings will be set to correspond to the completion of the twice yearly landscape analysis updates. The SP² will be co-chaired by one NIH and one academic researcher and will report to the PACT EC. Each member will have one vote; decisions will be made by simple majority. In the unlikely event that consensus cannot be achieved, conflicts will be raised to the EC for resolution. SP² operational logistics, staffing, and project management will be managed by FNIH.

PACT Executive Committee (EC)

The PACT EC will be responsible for oversight of PACT, ensuring that the partnership overall is conducted efficiently and in the best interests of patients and the public health, and for communicating the value of PACT to its partners and the public. Specifically, the EC will be responsible for the following:

1. Providing general guidance for the overall strategy of PACT within the rapidly changing oncology landscape.

2. Reviewing the progress of PACT on a regular basis and ensuring its effective and timely execution. This includes review and approval of major go/no-go milestones and funding changes.
3. Communicating the progress of PACT and any related challenges to the partners and the oncology community, and managing the relationships among the partners.
4. Establishing the policies that govern PACT and ensuring they are adhered to.
5. Overseeing the operation of the PACT JSC and SP², and resolving any conflicts or questions that they may not be able to resolve on their own.
6. Considering new initiatives or partners that may be added to PACT over time.

The membership of PACT (voting, except where otherwise noted) will include the following:

- ▶ The Director of the National Cancer Institute (or the Director of the Division of Cancer Treatment and Diagnosis) at NCI's discretion
- ▶ The Deputy Director of NCI
- ▶ The Director of CTEP, Division of Cancer Treatment and Diagnosis, NCI
- ▶ Two representatives from FDA (representing both CDER and CDRH)
- ▶ A patient advocate representative
- ▶ Three senior-level executives from three different biopharmaceutical company partners (head of research and development or global head of oncology research or development)
- ▶ A representative from the NIH Office of the Director (ex-officio, nonvoting)

The EC will be co-chaired by one senior official from NCI and one senior executive from one of the industry partners. It will meet at least quarterly by teleconference and will seek opportunities to meet periodically in person as schedules allow. Voting will be by simple majority.

To insure effective communications with and input from all PACT stakeholders, an Extended Executive Group, consisting of the EC members and representatives from the private sector partners not currently included on the EC, will be established to receive regular updates on PACT and advise the EC on its progress and direction. The Extended EC will meet twice a year by teleconference. The EC and the Extended Executive Group will be convened and supported by FNIH.

Consolidated Total Budget Estimate

The following table summarizes the budget inputs from Program Areas 1 and 2 into a single high level view of the total PACT budget:

CONSOLIDATED ITEMIZED PACT BUDGET				
ALL COSTS REFLECT TOTAL OVER 5 YEARS				
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)	TOTAL PROJECT COST	(b) (4)
Project 1.1 and 1.3.1	Create core laboratory network to conduct biomarker assays		\$64.5M	

CONSOLIDATED ITEMIZED PACT BUDGET				
ALL COSTS REFLECT TOTAL OVER 5 YEARS				
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)	TOTAL PROJECT COST	(b) (4)
Project 1.2	Create database to bank IO biomarker data from clinical trials		\$40M	

*Indirects lower for this project because a majority of work will occur at NCI and not academic institutions.

CONSOLIDATED ITEMIZED PACT BUDGET				
ALL COSTS REFLECT TOTAL OVER 5 YEARS				
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)	TOTAL PROJECT COST	(b) (4)
Project 1.3.2	Develop new IO biomarkers		\$40M	
Project 1.4	Standardize and harmonize biomarker assays for IO therapy		\$11.25M	

CONSOLIDATED ITEMIZED PACT BUDGET					
ALL COSTS REFLECT TOTAL OVER 5 YEARS					
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)		TOTAL PROJECT COST	(b) (4)
Project 1.3.2 and 1.4	Expand biorepository capabilities for sample storage			\$12.5M	
PROGRAM AREA 1				\$205.75M	
Project 2.1	Conduct biannual landscape analysis to determine priority biomarkers and combination therapies			\$1.15M	
	Compensate SP ² members for trial and biomarker landscape review			\$0.5M	

CONSOLIDATED ITEMIZED PACT BUDGET				
ALL COSTS REFLECT TOTAL OVER 5 YEARS				
PROJECT PLAN SECTION	BUDGET ITEM/ PROJECT GOAL	(b) (4)	TOTAL PROJECT COST	(b) (4)
Project 2.2	Co-fund high-priority combination clinical trials		\$27M	
Project 2.3	Conduct outreach and coordinate with other IO efforts			
PROGRAM AREA 2			\$28.65M	
FNIH Program Management Costs			\$16.6M	
PACT Initiative Total			\$251M	
Program Area 1—"Buy-up" Option				
Program Area 2—"Buy-up" Option				

Appendices

Appendix 1: Exploratory Biomarker Modules – Detailed Description

Evaluation of unknown biomarkers can be performed depending on availability of samples from the periphery and tissue and specific objectives of the relevant clinical trial. Various stakeholders (e.g., National Cancer Institute or company sponsor) can choose to fund these modules based on specific trial objectives or shared objectives across multiple studies.

Module 1c: Immune Cell Biology

As a potential expansion to the study of the immune cell biology to develop novel biomarkers, the PACT team suggest single-cell sequencing of tumor cells and immune cell subsets on a small number of tumors, such as myeloid-derived suppressor cells (MDSC), tumor-associated macrophages (TAM), neutrophils, T-cell clonality, and the use of newer technologies such as NanoString and CyTOF imaging, can be used to understand immune cell characterization, cell trafficking, and spatial co-localization of multiple cell types in the tumor microenvironment (TME).

Focus of the Project

Tumor and Periphery

- Analyze and compare different immune cell populations in the tumor and periphery (blood) by immunohistochemistry (IHC) and flow cytometry (or CyTOF) with standard operating procedures and quality-controlled experiments. Examples of potential markers are listed in Table A-1.

TABLE A-1: EXAMPLES OF CELL POPULATIONS

CELL POPULATIONS/MARKERS (EXAMPLES)

T cells (e.g., CD3, CD8, CD4, CD45RO, FoxP3, TIM3, LAG3, PD1, etc.)

NK cells (e.g., CD5, CD16, etc.)

B cells (CD19, activation markers, etc.)

Macrophages (e.g., CD163, CD206, CD64, etc.)

Dendritic cells (e.g., CD11c, CD1c, CDC141, HLA-DR, ILT7, etc.)

MDSCs (e.g., OLR1, CD15, CD14, etc.)

Neutrophils

Mast cells

Eosinophils

- ▶ Use similar marker set for flow cytometry and IHC, when possible:
 - ▷ Have multiple methods assessing same markers to ensure quality data.
 - ▷ Flow cytometry allows for quantification of immune cell subsets.
- ▶ IHC allows for analysis of localization of different immune populations (e.g., in T-cell- rich/ poor areas, edge, etc.).
- ▶ Depending on sample size, ability to do multiple panels will allow evaluation/quantification of larger number of markers than IHC. Will need to propose prioritized panels if sample is limiting.
- ▶ Functional cell analysis (e.g., T-cell and MDSC assays).
- ▶ Compare immune cell subsets in blood versus tumor.
- ▶ New assay formats allowing visualization of the 3-dimensional immune architecture of selected larger tumor samples (perhaps from pre-operative trials/window of opportunity trials) could be explored. This would expand knowledge obtained from standard IHC (Gerner, Kastenmuller, Ifrim, Kabat, & Germain, 2012; Gerner, Torabi-Parizi, & Germain, 2015).
 - ▷ Program infrastructure (clinical and bioinformatics) should be established with a view that technology combining assessment of molecular markers in the context of tumor (maybe tumor-draining lymph node as well) spatial architecture will evolve and will need to be incorporated in the future.

Module 2b: Cancer Genetics/Somatic Mutations

There are at least three high-priority expansion biomarkers that should be considered for answering specific questions related to DNA analysis: copy number alterations, single-nucleotide polymorphisms (SNP), and T-cell-receptor (TCR) and B-cell receptor (BCR) deep sequencing. Each of these should be employed as called for in relation to the mechanism of action of the therapy being tested.

Single-Nucleotide Polymorphisms (SNPs)

While still exploratory, germline SNPs that are associated with autoimmune disease may be useful to predict response or adverse events in cancer immunotherapy. One approach is to use SNP arrays to characterize established autoimmune markers. For example, genome-wide association studies have identified hundreds of SNPs associated with autoimmune diseases such as rheumatoid arthritis, lupus, and multiple sclerosis (Gregersen, Diamond, & Plenge, 2012). Immuno-oncology (IO) therapies alter the state of the immune system within the TME, and a major limitation is autoimmune adverse events. SNP genotyping will determine if the genetic predisposition to autoimmune disorders is predictive of response to IO therapy or adverse events. Ninety-five percent of 612 SNPs associated with 21 common autoimmune diseases can be genotyped using a combination of two commercially available SNP chips (MEG and Immune) from Illumina. These chips could be enhanced with additional SNPs associated with less common autoimmune disorders observed as adverse events during IO treatment.

TCR and BCR Deep Sequencing

Advances in genome sequencing technologies have also enabled the development of a new powerful platform for probing the adaptive immune systems (immunosequencing). Millions of TCR or BCR sequences can be read in parallel from a single sample by immunosequencing for the quantification of T- and B-cell clonal response in peripheral blood and tumor. The clinical application of immunosequencing for the diagnosis and monitoring of lymphoid malignancies demonstrated high sensitivity and specificity. The presence of tumor-infiltrated lymphocyte (TIL) correlates with a favorable clinical outcome. Emerging data suggest that both the number of TIL and degree of specific clonal expansions in pretreatment melanoma samples are predictive of response to anti-PD-1 therapy (Tumeh et al., 2014). TCR repertoire in peripheral blood correlates with immune-related adverse events in patients treated with immune checkpoint blockade. Immunosequencing biomarkers have the potential to help guide dose regimens and combination therapies. Moreover, for adoptive T-cell transfer or chimeric antigen receptor T-cell therapy, immunosequencing is used to identify novel tumor antigen/neoantigen-specific TCR and monitor the therapy itself by tracking the injected T cells. Immunosequencing has opened many avenues with the breadth of potential application in immunotherapy.

Module 3b: Transcriptomic Characterization of Microenvironment

Emerging technologies are making significant progress in characterizing the primary and acquired resistance mechanism for patients. Challenges include potential changes in RNA during the formation of single-cell suspensions that are required for current scRNA-seq protocols, low capture efficiency of cellular transcripts (10–15% using 3' poly-A capture), and limited sensitivity that makes detection of low-abundance transcripts unreliable. RNA-seq analysis of single functional cytolytic T cells with various immune phenotype markers provides additional information about the impacts of different molecules on cytolytic function, potentially to explore their correlation with clinical outcome.

Focus of the Project

Single-cell suspensions can be obtained from tumor samples where the tissue is processed with or without enzyme digestion, with a need to establish cell freezing media under a standard operation procedure.

No single marker will serve the purpose of transcriptomic characterization of the TME. Therefore, the main focus should be on comprehensive measurements of multiple baseline and on-therapy markers that are related to response and resistance to IO agents. Some of the currently available readouts include the interferon gamma signature, the cytotoxicity score, and mesenchymal or stemness tumor phenotype.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Whole-transcriptome profiling via next-generation sequencing (NGS) is recommended with baseline profiling at a minimum, and longitudinal samples for tumor indications where available are strongly encouraged.

- ▶ Peripheral blood mononuclear cell profiling is also recommended.
- ▶ Application of emerging single-cell characterization techniques are suggested to be explored and incorporated.

Emerging tissue processing approaches such as those that recover single nuclei for RNA-seq provide an opportunity to characterize immune subpopulations with unprecedented specificity. One advantage of single-cell techniques compared with bulk profiling is that the molecular features of rare subpopulations can be extracted and may help to identify novel targets. Another advantage is that one can clearly assess the relative frequencies of the various subpopulations such as T cells, T-regulatory cells, MDSCs, and TAMs.

In addition to providing an opportunity to characterize specific immune subpopulations within the TME, single-cell profiling can resolve cell subpopulations that are obscured by whole-tissue transcriptome profiling as well as their associated gene expression patterns and dynamics, and quantify cellular heterogeneity within a tissue, peripheral blood, fine-needle aspirate, or bone marrow aspirate.

Value Proposition

It is important to characterize the primary and acquired resistance mechanisms for patients who fail to respond to immune checkpoint blockade monotherapy, or transiently respond and then progress afterward. Transcriptomic profiling is one approach to identify these resistance mechanisms and guide combination clinical strategies, and can also be used to assess the impact of drug treatment to identify or validate pharmacodynamics markers of response.

Module 4b: Liquid Biopsy – Circulating Tumor Cells (CTCs), cfRNA, Exosomes

Focus of the Project

For the expansion biomarker module for liquid biopsy, we will look to develop techniques for better analyzing CTCs, cfRNA, and exosomes.

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Quantitative polymerase chain reaction (qPCR) – research tool that is readily translatable into commercial and regulatory viable *in vitro* diagnostic
- ▶ NGS – RNA-seq – good for biomarker discovery/research, laboratory-developed test approaches; also may be preferred technology in specific settings (e.g., detection of minimal residual disease in certain heme malignancies)
- ▶ Epic Biosciences and Rarecyte CTC platforms – selection agnostic CTC approaches; broader potential across many tumor types
- ▶ Exosome collection and subsequent DNA/RNA sequencing methods

Module 5: Defining the Role of the Microbiome in Modulating Cancer Immunotherapy Responses

Determinants of response to checkpoint blockade are under intense research and are likely to include immunosuppressive status in the TME as well as systemic priming status of the immune system.

Microbiome biomarker development is an active area of research that has already yielded intriguing results that have not only associated microbial population changes with oral, pancreatic, and colon cancer, but may also yield clues regarding the molecular mechanisms linking microbial interactions with these and other types of tumors (Linares, Gustafsson, Baquero, & Martinez, 2006; Schloissnig et al., 2013).

At present, there are no human datasets linking microbiome changes with anti-tumor responses. However, some intriguing recent preclinical studies suggest that the microbiome is required for the anti-tumor activity of anti-PD-L1 and anti-CTLA4, as these antibodies lack their efficacy in mice devoid of microbiota, and the efficacy is transmissible to poor-responder mice via the microbiota. Although we are at a very early stage in this field, these animal studies suggest that systemic immunity is in part regulated by the microbiome.

Value Proposition

Since human data are fundamental to start to address the role of the microbiome in cancer immunotherapy, we propose to stimulate prospective studies in patients undergoing immunotherapy. The principal activity will focus on bacterial communities measurable in fecal samples. Potentially, this project could be expanded to include multiple microbial communities across different mucosal surfaces.

Microbes as Biomarkers

Well-characterized and validated biomarkers of disease can be used for cancer detection and diagnosis, or to measure patient response to therapeutics, and may also provide a rationale for choice of therapy.

The importance of developing microbiome-based patient phenotypes is supported by recent studies demonstrating that when gut bacterial communities are compromised, immunotherapy and standard chemotherapy regimens may lose efficacy (Iida et al., 2013; Viaud et al., 2013). Thus, a detailed knowledge of each cancer patient's unique microbiome could have high translational value to clinical practice since this information could be exploited for the purposes of optimizing individual therapeutic responses, possibly by altering microbial signals to change host metabolic regulation or by developing new metrics for patient stratification based upon matching therapeutic agents with an individual's microbial metabolism or immune profile.

Focus of the Project

Depending on the clinical application, microbiome-based biomarkers may be developed by examining various features and readouts, alone or in combination with existing biomarkers. For example, advanced *in silico* techniques have been used to analyze individual metagenomic profiles as a molecular biomarker that may identify pathogenic or drug-resistance collective phenotypes (Zackular, Rogers, Ruffin, & Schloss, 2014).

Indeed, a current clinical trial (NCT02141945) is testing a metagenomic-based diagnostic tool for patients with colonic neoplasia.

Other strategies have been devised to associate specific tumor/microbe interactions that include the following:

- ▶ Analysis of whole-organism presence/abundance
- ▶ Detection/quantification of biosynthetic products (outer membrane vesicles, miRNA, toxins, lipopolysaccharide [LPS])
- ▶ Detection/quantification of microbial metabolites (short-chain fatty acids [SCFAs], 2-HG, bile acids)
- ▶ Molecular signatures of host responses to altered microbiomes

Thus, colonic hyperpermeability and pro-inflammatory cytokine profiles that are associated with specific bacterial taxa could be used to identify individuals at risk for disease progression or poor therapeutic response.

Potential biomarkers that PACT could expand to test are:

- ▶ Levels of bacterial taxa (16S sequence data)
- ▶ Levels of bacterial metabolites (SCFAs, bile acids, etc.)
- ▶ Levels of bacterial enzymes (β -glucuronidase (GUS), bile acid hydrolases, etc.)
- ▶ Levels of serum LPS, muramyl dipeptide
- ▶ Host inflammatory cytokines/host molecular signatures of dysbiosis

Experimental Screening Platforms To Include and Purpose for Each:

- ▶ Enzyme activity screens (480-well) for detecting bacterial enzyme levels
- ▶ Microarray or enzyme-linked immunosorbent assay for detecting cytokine profiles
- ▶ High-throughput mass spectrometry for detecting bacterial metabolites
- ▶ Quantitative immunohistochemistry for detecting immune checkpoint receptor levels after probiotic treatment

Module 6: Non-Immune Cell Characterization of Tumor Microenvironment (Differentiation, Stroma, Vasculature, Etc.)

Tumor resistance and immune evasion are influenced tremendously by the surrounding nonimmune microenvironment that can include stromal cells, blood vessels, and small particles (e.g., exosomes, ectosomes, microvesicles), cytokines, and enzyme or adhesive properties that are derived from these. These have distinct roles based upon the type of cancer (solid tumor versus hematologic disseminated tumor) and intrinsic driving tumor biology.

Focus of the Project

PACT could use the following as a starting point for expansion biomarker modules:

- ▶ Small particles (exosomes, ectosomes, microvesicles) from blood and the TME.
- ▶ Antibodies that selectively separate mesenchymal stromal cells from tumor and hematopoietic immune cells and strategies to isolate these for single-cell molecular characterization.
- ▶ Markers of blood vessels (i.e., CD34, CD31 and endoglin), effective angiogenesis, and tumor hypoxia and strategies to accurately quantitate these in relevant models.
- ▶ The representative nonimmune cell genes (DNA and RNA) could be used to assess the signature of vasculature, stroma, and other nonimmune cells in the TME. It is of importance to explore their correlation with tumor and immune cell-derived signature in the same tumor, as well as clinical outcome.
- ▶ Baseline serum vascular endothelial growth factor (VEGF) demonstrated the correlation with clinical outcome in melanoma patients treated with CTLA-4 blockade.
- ▶ Combination anti-VEGF with checkpoint blockade showed better clinical response in patients with melanoma and renal cell carcinoma.

Experimental Screening Platforms To Include and Purpose for Each:

As small particles and their contents will be mixed in blood, technologies that separate these based upon distinct antigens expressed by the releasing nonimmune microenvironment cells will be important.

If canine models of spontaneous cancer are chosen to study this, it will be necessary to establish the reagents compatible with exosome (and other small particle separation) and also IHC and separation strategies for other types of stromal cells.

Imaging strategies that allow examination of intracellular exosomes and their trafficking along with adhesive properties of tumor and stromal cells will be important.

Support of a comprehensive center to study this in the setting of spontaneous canine tumors or another large animal model will be needed.

Value Proposition

While features related to tumor vasculature and angiogenesis have been extensively studied and therapeutics directed toward this successfully, our understanding of the other components of the nonimmune microenvironment is at an elemental stage. Furthermore, animal models available to study this are very limited. An opportunity to study these interactions comes potentially from the many solid and hematologic spontaneous mouse models and also companion canine models of cancer where serial sampling of tumors can occur and sufficient blood volume can be obtained to study soluble factors as well. Early clinical data showed that combination immune checkpoint blockade with the agents to overcome nonimmune-cell-derived suppression potentially achieved a synergistic, favorable clinical response.

Appendix 2: Additional Assay Standardization and Harmonization Examples

PDL-1 IHC Comparability Example

An example of a collaboration that addresses comparability of assay approaches across multiple immunohistochemistry (IHC)-based PD-L1 tests is the Blueprint PD-L1 IHC Assay Comparison Project developed by four pharmaceutical companies (Bristol-Myers Squibb, Merck & Co. Inc., AstraZeneca PLC, and Genentech, Inc.) and two diagnostic companies (Agilent Technologies, Inc./Dako Corp and Roche/ Ventana Medical Systems, Inc.) in collaboration with the International Association for the Study of Lung Cancer and the American Association for Cancer Research (AACR). The project aims to cross compare four different diagnostics, including U.S. Food and Drug Administration (FDA)-approved tests, for detection of PD-L1 expression in tumor tissue (Averbuch et al., 2015). The PD-L1 IHC 22C3 pharmDx test was approved as a companion diagnostic to pembrolizumab as a single agent in second-line nonsmall-cell lung cancer (NSCLC). The test was used to determine patient eligibility in a single arm study KEYNOTE 001. The PD-L1 IHC 28-8 pharmDx test was approved by the FDA as a complementary test to another PD-1 inhibitor, nivolumab, in the nonsquamous nonsmall-cell lung cancer (NSCLC) and melanoma patient populations. The scope of the Blueprint Project was to establish technical comparability between the assays. Preliminary results of this effort were presented at the 2016 AACR annual meeting. Analyses from the Blueprint Project confirm that there is high concordance for the two approved PD-L1 diagnostics in NSCLC (American Association for Cancer Research, 2016; Hirsch et al., 2017).

Assay Harmonization Effort Examples

Currently, there are several ongoing initiatives to coordinate and harmonize immunoprofiling efforts including the Human Immunology Project, Minimal Information About T Cell Assays (MIATA), human leukocyte antigen-peptide multimer assays, and others (Britten et al., 2009; Britten et al., 2012; Maecker et al., 2010; Maecker, McCoy, & Nussenblatt, 2012; Mandruzzato et al., 2016).

Other technologies, such as gene expression microarrays, have achieved a reasonable degree of standardization led by consortia such as the Microarray Quality Control (Patterson et al., 2006), the External RNA Controls Consortium (Devonshire, Elaswarapu, & Foy, 2010), and the EMERALD project (Beisvåg et al., 2011).

Another example of assay harmonization to minimize data variability and allow worldwide correlations is the Immunoscore initiative (Galon et al., 2012). Effective large-scale assay harmonization efforts have been conducted for IHC-based immunological assays of immune cell populations in formalin-fixed paraffin-embedded (FFPE) tumor sections. The Immunoscore includes the immune cell density, calculated by numerical quantification of two lymphocyte populations, cytotoxic and memory T cells at the tumor center, and the invasive margin of tumors. This criterion has the potential to establish prognosis of patient clinical outcome,

regardless of the absence of other cancer-associated prognostic markers, such as in early tumor stage (I/II) patients. Importantly, it will need to be validated as a predictor of response for immunotherapy.

Pre-analytical Considerations for Standardization of Key Assays

Pre-analytical processing of samples for diagnostic assays including those used for single-cell immune response assays, such as ELISpot or flow cytometric analysis, includes patient-related factors such as tissue-ischemia time, pretreatment with drugs, dynamic nature of the analyte, and sample heterogeneity. Analyte stability can be affected by the sample collection process including anticoagulants and preservatives used for blood draws, freezing/thawing conditions, time between collection and testing, and storage conditions before processing (Mallone et al., 2011).

IHC, the most widely used platform for biomarker assessment in diagnostic surgical pathology and for retrospective research, is a multistep process that requires standardized conditions for tissue collection, fixation and processing, preparation of the IHC slide, and interpretation of the staining results. IHC-based assays remain important tests as complementary diagnostics and companion diagnostics to assess antigen expression on diagnostic or surgical specimens for selecting patients for specific targeted therapies (e.g., HER2 expression for Herceptin), and more recently PD-L1 measurement as a companion diagnostic for pembrolizumab treatment of NSCLC patients. Published guidelines for measuring established biomarkers such as estrogen receptor, progesterone receptor, and HER2 are available (Hammond et al., 2010). General guidelines, including analyte stability and laboratory quality control, for performing analysis of tissue-based molecular biomarkers have been published (Cree et al., 2014).

Next-generation sequencing tests for tumor mutation analysis, similar to other complex molecular diagnostic tests, should demonstrate adequate analytical performance. It should follow standard operating procedures that specifically address materials and procedures including patient's sample type, method of nucleic acid extraction, as well as technical metrics for nucleic acid quantification and quality, which can negatively impact on sensitivity and reproducibility of the assay (Pant, Weiner, & Marton, 2014; Rehm et al., 2013).

The preparation of intact and pure mRNA is one of the key factors in mRNA gene quantification using gene expression profiling of RNA sequencing. Extraction of nucleic acids and particularly RNA is very sensitive to nucleases. Thus, nuclease free conditions should be implemented to control variability in steps such as sample collection, tissue fixation, and FFPE block handling including sectioning. For the extraction of nucleic acids from the FFPE tumor tissue, a method for the simultaneous isolation of high-quality DNA, RNA, and microRNA as well as protein from the same sample has been developed (Kalmar et al., 2013).

Appendix 3: The PACT Design Team

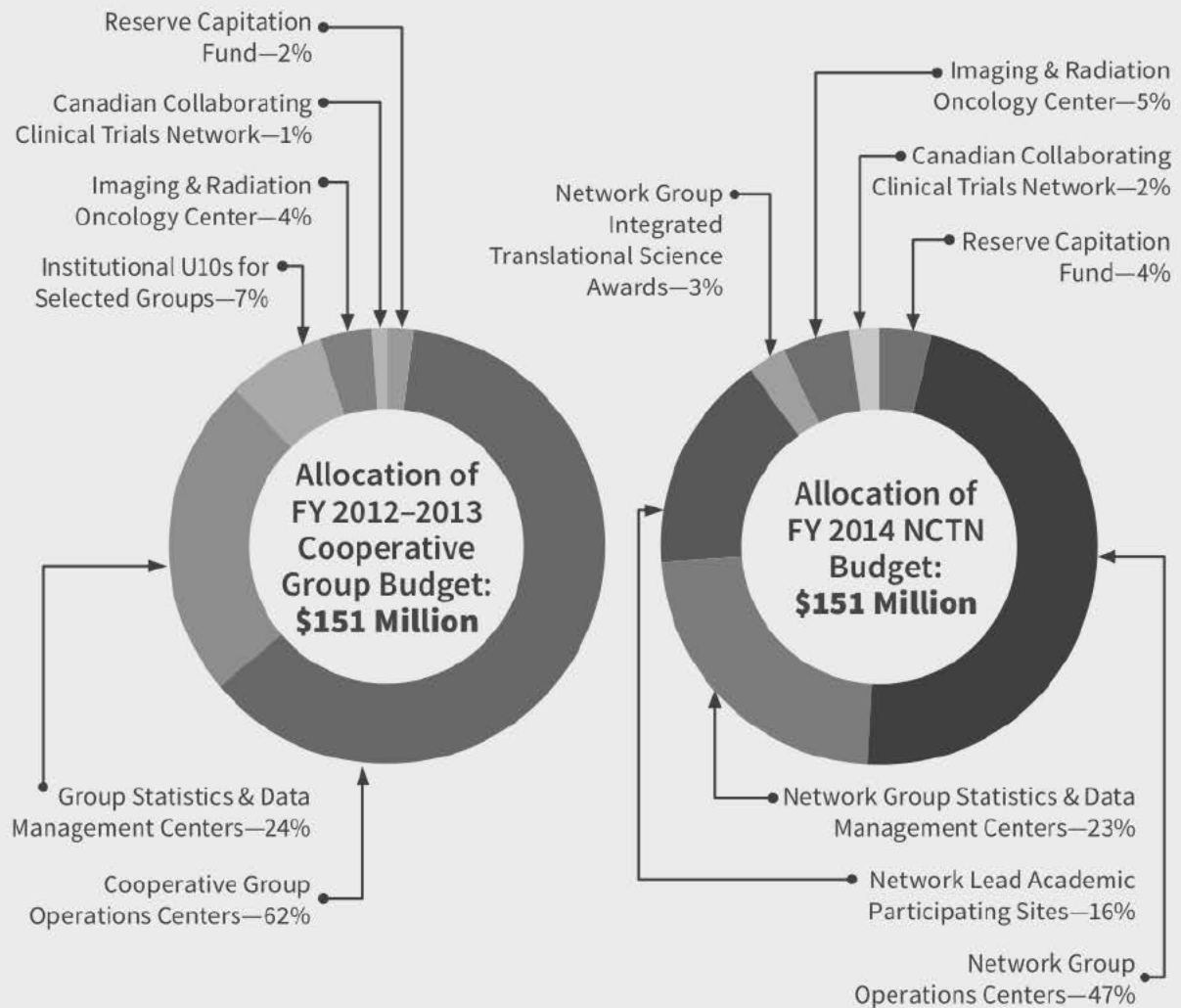
INDUSTRY PARTICIPANTS	Jeff Engelman (Novartis)—Industry Co-Chair		Axel Hoos (GSK)—Industry Co-Chair	
	Bob Abraham (Pfizer)	Matthew Albert (Genentech)	Carl Barrett (AstraZeneca)	Olaf Christensen (EMD)
	Ute Dugan (BMS)	Jeff Ecsedy (Takeda)	Jessie English (EMD)	Howard Fingert (Takeda)
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	Greg Plowman (Lilly)	Chandra Ramanathan (Bayer)	David Reese (Amgen)	Paul Rejto (Pfizer)
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	Rebecca Baker (NIH)	Gideon Blumenthal (FDA)	Kevin Howcroft (NCI)	Tony Kerlavage (NCI)
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PACT PROGRAM MANAGEMENT	Stacey Adam (FNIH)	David Wholley (FNIH)		

Appendix 4: Detailed Description of the Cancer Therapy Evaluation Program (CTEP) – National Clinical Trials Network (NCTN)

The NCTN Budget

The overall NCTN budget for these awards is \$151 million. This amount is the same as the total budget provided to the Cooperative Groups for awards in each of fiscal years (FY) 2012 and 2013, despite the substantial reductions in the National Cancer Institute (NCI) budget that resulted from sequestration starting in 2013. What has changed, however, is the distribution of funds to the various components of the NCTN, as compared with the components of the former Cooperative Group program.

The distribution of funds to the Network Group Operations Center grants changed from 62 percent in FY 2012 and 2013 to 47 percent in FY 2014 due to the consolidation of the infrastructures of the Operations and Statistical Centers; funding of new components in the NCTN, including the Lead Academic Participating Sites and Integrated Translational Science Awards; and expansion of the Imaging and Radiology Oncology Group for the entire network. The new system provides for an annual enrollment of about 17,000 patients on interventional trials, a 15 percent reduction compared with about 21,000 enrolled patients in recent years. This reduction is anticipated to occur gradually over 2 to 3 years. To this end, NCI reserved funds to distribute to the NCTN groups later in FY 2014 to accommodate an enrollment of about 21,000 patients.

COMPARISON OF COOPERATIVE GROUP PROGRAM FUNDING AND NCTN PROGRAM FUNDING**Funding Precision Medicine Trials**

NCI believes that reducing the budget of the Network Group Operations Centers will not impede the NCTN's ability to perform important trials. Conducting the new generation of clinical trials requires new technologies and procedures, including tissue collection (fresh biopsy samples are often necessary), advanced DNA and RNA sequencing methods with rapid turnaround times, and complex analytic algorithms to distinguish normal genetic variants from tumor-specific changes. These, in turn, entail new expenses for surgery, interventional radiology, molecular pathology, and bioinformatics that have not typically been a part of clinical trials.

However, although the screening tests may need to be performed on very large numbers of patients to find those whose tumors exhibit the appropriate molecular profile, the numbers of patients required for interventional studies are likely to be smaller than what was required in previous trials.

That is because the patient selection is based on having the target for the new therapy, leading to larger differences in clinical benefit (such as how long patients live overall or live without tumor progression) between the intervention and control groups. Thus, future clinical trials will, in many cases, require fewer numbers of patients due to the selection of patients most likely to benefit from the intervention being tested.

Although screening patients for tumors with specific molecular characteristics may require large numbers of patients, the screening components of studies are less costly than the actual interventional study. Hence, clinical trials in the future are likely to involve screening components, which will be reimbursed at a lower rate, with smaller interventional components that will be reimbursed at higher rates. More precision in patient selection will permit study designs that can aim for larger therapeutic effects and thereby further decrease the size of trials.

Efficiencies in Collaboration

These changes will, however, require the NCTN groups to function differently compared with how they functioned in the previous system. For example, NCTN groups should be able to reduce the costs of conducting trials by sharing resources. If a particular group has many active trials, it may have to decrease the number of new trials it is planning. Groups with fewer active trials can take up those new trials instead. This collaborative approach should allow members of one NCTN group to support trials led by other groups and should afford NCTN members an ability to conduct a full portfolio of trials in the most common cancers.

Because the NCTN has only four U.S. adult groups, with fewer Operations and Statistical Centers that require financial support, some savings are anticipated. This consolidation was planned for over the past several years, and NCI provided \$24 million in funding supplements to the newly consolidated groups to help them absorb the costs of their ongoing trials as well as to fund the integration of their separate infrastructures.

NCI also provided more than \$40 million in other funding supplements to transition all the groups to a common data management system (Medidata Rave®), develop an integrated IT system for the tissue banks, and implement specific precision medicine clinical trials.

Additional Support

For the past several years, NCI has provided significant additional annual support for the Cooperative Groups and will continue to provide these funds for the NCTN, in addition to the grant funding described above. Clinical trials are complex undertakings that require a host of support organizations and funding streams. The new system includes a number of other features that are not included in the NCTN awards but are essential to carrying out the NCTN mission.

The additional support includes:

- Central Institutional Review Boards, an important component of NCI's clinical trials system that has added speed, efficiency, and uniformity to ethics review.

- ▶ The Cancer Trials Support Unit, an NCI-funded contract that provides clinical investigators and their staff with one-stop online access to NCTN trials and allows investigators to register new patients.
- ▶ A dedicated tissue bank for each Network group funded through a separate NCI award mechanism.
- ▶ The Biomarker, Imaging, and Quality of Life Studies Funding Program, a separate funding stream for NCTN trials that supports correlative science studies on group trials. NCTN groups compete for funds that are specifically reserved annually for this purpose. The availability of dedicated funds greatly facilitates coordination as clinical trials must meet stringent deadlines.
- ▶ In addition, approximately one-quarter of patient accrual on NCTN treatment trials is paid for by the NCI Community Oncology Research Program (NCORP; previously the Community Clinical Oncology Program/Minority-Based Community Clinical Oncology Program). The community hospitals and medical centers participating in the NCORP are reimbursed for accruing patients to NCTN treatment trials by their NCORP awards, not via the NCTN Group Operations award.

ADDITIONAL ANNUAL NCI SUPPORT	
NCI Central IRBs (Adult & Pediatrics)	\$4.5 Million
Cancer Trials Support Unit	\$14.0
Tissue Banks	\$8.6
Biomarker, Imaging, and Quality of Life Studies Funding Program	\$10.0
NCORP Support for NCTN Treatment Trials (Estimated)	\$33.1
\$70.2 Million*	

Other NCI support includes but is not limited to:

- ▶ Operations of common data management system (Medidata Rave®)
- ▶ Clinical trials auditing
- ▶ Drug storage and distribution
- ▶ Regulatory oversight (CTEP IND Studies)

*This is an approximation and is dependent on annual NCI appropriations.

Finally, in addition to these substantial annual expenditures, NCI also subsidizes the NCTN by paying for many other essential clinical trial functions, thereby further reducing costs borne by the Network groups:

- ▶ NCI will pay for the licenses and hosting fees of the electronic, common data management system, called Medidata Rave®, used by all NCTN groups.
- ▶ NCI will oversee a national audit system for NCTN trials.
- ▶ NCI will manage Investigational New Drug applications to the U.S. Food and Drug Administration along with the distribution of these drugs for many NCTN trials.

It is estimated that support for these activities costs NCI approximately \$15 million annually.

<https://www.cancer.gov/research/areas/clinical-trials/nctn/budget>

Appendix 5: Active NIH/NCI Requests for Applications (RFAs) Relevant to PACT

2017

1. CA17-009 Mechanisms of Cancer Drug Resistance and Sensitivity (U54)
2. CA17-006 Cancer Immunologic Data Commons (CIDC) (U24)
3. CA17-005 Cancer Immune Monitoring and Analysis Centers (U24)
4. CA17-013 Advanced Development and Validation of Emerging Biospecimen Science Technologies for Basic and Clinical Cancer Research (R33)

2016

5. CA16-501 Limited Competition: Cancer Immunotherapy Trials Network (CITN)(UM1)

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Executive Summary

Recent advances in cancer treatment have offered the prospect of greatly enhanced outcomes, prolonged survival, and cure for some patients. Much of the recent success has been driven by the development of new immuno-oncology (IO) agents, leading to an explosion of translational research as well as investment in the field. To date, however, the improvements in outcomes and cure generated by the monotherapies of these agents are possible only for a minority of patients, and emerging data demonstrate that the greatest impact on cancer treatment will be achieved by combinations of multiple IO agents or of IO and non-IO agents. The successful pursuit of these combination therapies is complicated, however, by the sheer numbers of possible combinations, by high biologic complexity, and by the need for new translational biomarkers and assays to guide which patients should receive which combinations. These challenges are further compounded by the novelty and intensely competitive nature of the IO field, which has encouraged fragmented and at times duplicative research approaches.

To solve these challenges, a systematic cross-sector effort is required to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations. The magnitude of this task and the substantial current knowledge gaps within the field make it unlikely a single stakeholder can execute such a mission alone. As a part of its support of the Cancer Moonshot, the National Institutes of Health (NIH) has proposed a 5-year, ~\$250 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) to enable achievement of these goals. The initial strategic plan for PACT has been developed through a process led by the Foundation for the NIH (FNIH) with input from 42 key opinion leaders in the cancer field, encompassing representatives from the National Cancer Institute (NCI), U.S. Food and Drug Administration (FDA), academia, and 15 industry partners—AbbVie, Amgen, AstraZeneca, Bayer, Boehringer-Ingelheim, BMS, EMD Serono, Genentech, GSK, Lilly, Merck, Novartis, Pfizer, PhRMA, and Takeda.

PACT aims to accelerate the development of effective combination therapies by enabling critical clinical investigations not covered by others, unifying clinical biomarker investigation, filling knowledge gaps, and integrating information from multiple sources, through two programs:

Program 1: Facilitate robust, systematic, and uniformly conducted clinical testing of basic biomarkers that enable researchers and clinicians to better understand the mechanisms of response and resistance to treatment strategies. PACT will provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by providing standardized biomarker modules, which can be utilized within the PACT programs and across the research community. These modules allow for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination immunotherapies and related combinations. Specific elements of the program include the following:

- Providing a set of basic biomarker modules for uniform clinical application.
- Establishing a network of 3–5 core laboratories to coordinate, conduct, validate, and standardize biomarker assays. Funding the development of standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance.
- Incorporating biomarkers and data collection standards into trials prioritized through PACT and coordinating their adoption broadly across the IO research community.
- Creating a comprehensive database that integrates biomarker and clinical data to enable pre-competitive correlative biomarker analyses.

Program 2: Provide scientific coordination for the selection of clinical combination therapy trials important to the field but not already being performed elsewhere, and co-fund such trials with partners. This will be accomplished by the following:

- Creating and maintaining a “landscape analysis” of combination therapy trials and biomarkers across the entire IO and oncology space, enabling categorization of prospective new trials based on relevance.
- Selecting and co-funding high relevance combination trials not being performed by other entities, while leveraging significant existing investments (such as in trial networks) made by the government, companies, and nonprofit foundations.
- Facilitating information sharing by all stakeholders to better coordinate clinical/translational oncology programs, align investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted. This will include active outreach to other IO research efforts on an ongoing basis.

The core laboratory, assay development, and database functions required as part of Program 1 will be built on a solid base of research infrastructure and academic grants funded by NCI. Fortunately, NCI has recently released several Requests for Applications (RFAs) in November 2016 that are highly germane to the core goals of PACT (see Appendix 5). Based largely on existing funding from the Precision Oncology Initiative, with additional planned Cancer Moonshot funding, these RFAs seek

applications for ~\$110 million in funding over 5 years beginning in 2017 for a number of Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational, and computational expertise. Although currently limited as to the number of sites, assays, and data types supported, these grants provide a “shovel ready” foundation for the core lab and database functions required by PACT, particularly when combined with NCI’s recently announced Formulary initiative and its existing national clinical trials network and genomic data management programs.

In addition to supporting these resources, PACT will coordinate and standardize use of existing standardized biomarker assays to most efficiently use available resources. If available, fully validated existing biomarker assays can be conducted through parties outside PACT but channel data into the PACT database, provided assays are performed to PACT standards.

(b) (4)

A joint governance structure will maintain close involvement by all partners in key decisions, consisting of:

- An operationally focused PACT Joint Steering Committee (JSC) to direct the research plan and ensure adherence to project milestones
- A PACT Scientific Project Selection Panel (SP2) to analyze potential therapy/biomarker combinations and advise the JSC regarding fundable PACT studies
- A PACT Executive Committee (EC) to provide strategic direction, communication with partner leadership, and resolution of policy issues.

Voting participation in the JSC and EC will be split 50/50 between government and private sector partners. The SP² will consist of key academic/NCI oncology experts and scientists with industry oncology experience in drug development who lack significant financial and employment ties to individual companies in order to ensure its advisory role is carried out with objectivity and transparency.

All PACT data will be released publicly as promptly and broadly as possible in keeping with NIH’s mission and policy, though also dependent on restrictions in underlying clinical trial and grant agreements. Where feasible, PACT participants will have early access to data, but consistent with these restrictions.

The value proposition for PACT stakeholders, for the oncology field, and for patients will be considerable, providing immediate:

- Access to standardized immune biomarker modules, enabling a systematic and uniform analytical approach across trials
- Access to databases of pre-competitive biomarker analyses, accelerating hypothesis testing and decision-making
- Access to core facilities with standardized analysis platforms, procedures, and best practices, working with regulatory agencies to ensure the highest quality evidence and documentation, relevant to potential registration and labeling
- Access to clinical trial landscape analyses for combination therapies and biomarkers across the entire IO space, and the opportunity to align research priorities, avoid duplication of effort, fill gaps, and share resources
- Opportunities to initiate high relevance trials with company assets for PACT co-funding
- Opportunity to drive new collaborations resulting from PACT insights and contribute to improving cure rates for patients under the goals of the Cancer Moonshot Initiative

(b) (4)

Once key partners are confirmed, FNIH will reconvene the scientific leads from committed partners to develop a final research plan, including detailed project plans and go/no-go milestones. Given the sense of urgency in addressing patient needs, the timing of NIH funding, and the rapid pace of progress in the field, formal launch of PACT is being targeted for Q3 of 2017.

From: Wholley, David (FNIH) [T]
Sent: Mon, 20 Mar 2017 12:19:59 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: Draft note to [REDACTED] (b) (4)

(b) (5)

From: Wholley, David (FNIH) [T]
Sent: Mon, 23 Oct 2017 00:50:39 +0000
To: McManus, Ayanna (NIH/OD) [E]; Wood, Gretchen (NIH/OD) [E]; Boskent, Celeste (NIH/OD) [E]; Di Mantova, Emma (NIH/OD) [E]; Collins, Francis (NIH/OD) [E]
Cc: Hoffmann, Steve (FNIH) [T]; Menetski, Joseph (FNIH) [T]; Vardanian, Lilit (FNIH) [T]; Canet-Aviles, Rosa (FNIH) [T]; Cush, Stephanie (FNIH) [T]; Melencio, Cheryl (FNIH) [T]; Morgan, Emily (FNIH) [T]
Subject: Draft of slides for discussion on tomorrow's AMP EC pre-call
Attachments: AMP EC Slides Oct 27-Draft.pptx, 2017_08_25_AMP EC teleconference final.docx
Importance: High

This is what I have so far for tomorrow's call. Still awaiting review/inputs from some of the co-chairs. Look forward to our discussion.

(b) (6) Expect I will be able to call in and moderate the EC call, but if for any reason I am unable to (it will be 6AM where I am, and not a familiar environment) Joe Menetski is prepared to lead the call from the FNIH side without me.

Thanks, David

David Wholley
Director, Research Partnerships
Foundation for the National Institutes of Health
(301) 594-6343
fnih.org

Learn more about the FNIH in our 2016 Annual Report: fnih.org/AnnualReport.

Accelerating Medicines Partnership Executive Committee Update

27 October, 2017



NIH - 002

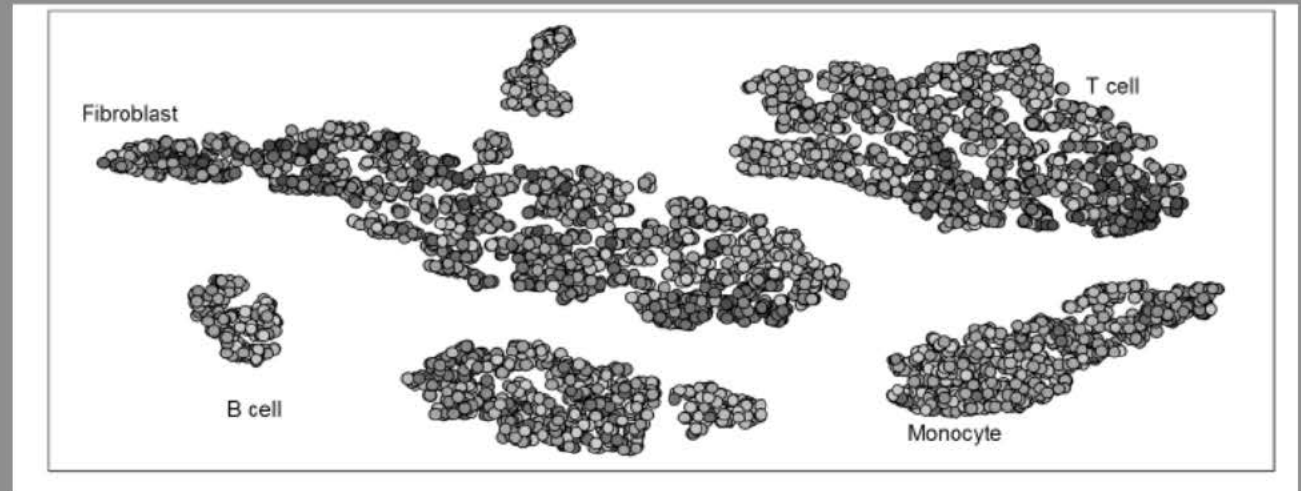


Contents

(b) (5)



Accelerating Medicines Partnership RA/SLE



FNIH

Foundation for the
National Institutes of Health

NIH - 002582



Accelerating Medicines Partnership Alzheimer's Disease



FNIH

Foundation for the
National Institutes of Health

NIH - 002597



Upcoming activities:

(b) (5)

Accelerating Medicines PartnershipType 2 Diabetes

DRAFT slides awaiting first review by co-chairs



FNIH

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National Institutes of Health

NIH - 002609



Accelerating Medicines Partnership Parkinson's Disease Program Development



FNIH

Foundation for the
National Institutes of Health

NIH - 002619



Upcoming EC meetings

- **Next MeetingAMP EEC: Friday, December 15 from 7:00 am – 8:30 am**

**Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)**

Executive Committee (EC)

Teleconference Meeting Minutes

Friday, August 25, 2017

7:00 – 8:00 a.m. ET

Participants

Michael Biarnes (FNIH), Neil Buckholtz (NIH/NIA), Bob Carter (NIH/NIAMS), David Collier (Lilly), Francis Collins (NIH), Stephanie Cush (FNIH), Mikael Dolsten (Pfizer), Tanya Fischer (Sanofi), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), Jan Lundberg (Lilly), Joseph Menetski (FNIH), Laurie Ryan (NIH/NIA), Susana Serrate-Sztejn (NIH/NIAMS), Philip Smith (NIH/NIDDK), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), Lilit Vardanian (FNIH), David Wholley (FNIH)

(b) (4), (b) (5)

Final Remarks/Adjourn

- Mr. Wholley announced that next meetings are scheduled as follows:
 - EC meeting: October 27, 2017 (7 a.m. Eastern Time)
 - Extended EC meeting: December 15, 2017 (7 a.m. Eastern Time)
- Mr. Wholley adjourned the meeting.

From: Wholley, David (FNIH) [T]
Sent: Tue, 17 Oct 2017 04:28:35 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Baker, Rebecca (NIH/OD) [E];Porter, Linda (NIH/NINDS) [E];Menetski, Joseph (FNIH) [T];Biarnes, Michael (FNIH) [T];Melencio, Cheryl (FNIH) [T]
Subject: email drafts for opioids partnership
Attachments: Opioid_FC email to Ind CoChair_101617dw.docx, Opioids email to partner reps_10-16-17.docx, Opioids FC email to FA2 academics with NIH history_10-16-17.docx, Opioids FC email to FA2 academics_10-16-17.docx

Francis,

Here are the emails I have composed for

1. (b) (5) the lead industry co-chair identified by Walter and Linda for Focus Area #2. Note that we are still waiting to see if Nora wants an industry co-chair for area #1.
2. Invitation to all industry reps to participate in the partnership generally and the Friday call specifically. Note you may need to adjust how logistics info for the call is handled—I think we will need Rebecca's help here. The note would be sent to the attendees on the lists provided to Rebecca by Bill Chin.
3. An invitation to academic invitees to work on focus area #2 who attended one of the NIH workshops over the summer. Again, we would need to see Nora's plan and whether she wants such invitees for focus area 1 before proceeding.
4. An invitation to academic invitees to work on focus area #2 who did NOT attend any of the NIH workshops and are newer to the process.

The academic invitees for notes 3 and 4 are:

(b) (5)

We are working to find their email addresses, but I am copying Linda Porter to see if she can provide them faster. Linda, I assume Francis should start with (b) (5)
DeBar, and then based on the outcome of Friday's call we can invite (b) (5)

(b) (5)

Thanks, David

David Wholley
Director, Research Partnerships
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*Learn more about the FNIH in our **2016 Annual Report**: fnih.org/AnnualReport.*

From: Wholley, David (FNIH) [T]
Sent: Sat, 8 Apr 2017 10:48:53 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Canet-Aviles, Rosa (FNIH) [T]; Sutherland, Margaret (NIH/NINDS) [E]
Subject: Emailing - Technical Plan for AMP PD knowledge portal.pdf
Attachments: Technical Plan for AMP PD knowledge portal.pdf

Francis: This is the technical plan we shared with Verily. It is a little hard to tease out but it seems the core databases (PPMI, Harvard Biomarker Study, PDPB) total today about 3500 cases and 6000 controls. I have asked Rosa Canet-Aviles and Marg Sutherland to weigh in directly on this in the interest of time.

Technical Plan for AMP-PD Knowledge platform

Introduction:

The Accelerating Medicine Partnership (AMP) in Parkinson's Disease (PD) is a proposed partnership between the National Institutes of Health, industry partners and non-government organizations with the goals of executing innovative research that advances the identification and validation of new therapeutic targets for drug development and developing biomarkers that will support better clinical trial designs in PD.

The two projects that comprise the AMP-PD program; 1) Target and Assays, and 2) Clinical Biomarkers to enable Proof-of-Concept Trials. These projects are designed to be interactive, and it is anticipated that data derived from one project will help to inform directions and strategies used in the other project. The complementary nature of the 2 projects is based on shared approaches and platforms for whole genome sequencing, RNA preparation and sequencing, epigenomic analysis, proteomic and metabolomic techniques for data generation and harmonization of clinical data from multiple biomarker cohort studies that include detailed longitudinal assessment of over 5,000 PD cases and age and gender matched controls with fluid biosample collections. The key element that will link AMP-PD projects 1 and 2 and provide the interface for data access and analysis for AMP-PD investigators and the larger research community will be the AMP-PD Knowledge Platform.

The AMP-PD Knowledge Platform will support data sharing and analysis through a cloud-based infrastructure that integrates systems and tools through a common interface, and links various data types including:

- clinical data and associated imaging data
- whole genome and exome sequencing data
- RNA sequencing (RNA seq) data
- robotics imaging data
- proteomics and metabolomics mass spectrometry data
- epigenomic data
- metadata from biomarker platforms like studies, protocols, forms, cohorts, subjects, and publications

To ensure data quality and address the needs of multiple data science stakeholders, both raw and processed data will be stored in the cloud environment and quality control of data will be coordinated through the use of standardized form structures with quality control checks that include variant ranges and types built into the form structure data elements. Common data analysis pipelines are predominantly based on current large whole genome sequencing consortia strategies and various NIH Common Fund data coordinating center quality control and analysis strategies for RNA seq, proteomics, epigenomics and metabolomics data. These pipelines will be used to generate processed datasets that will be available to researchers both within and outside of AMP-PD. These processed datasets will be described and published to discovery indexes, like the NIH Big Data to Knowledge (BD2K) DataMed, and will also be used to generate a searchable aggregate database on a public site that can provide summary information, as an entry point for data discovery, for less data intensive users. Additional open source integrative data analytical tools will also be available in the cloud environment to support integrative analysis of the various data types. A cloud collaborative project management solution will be designed

to support collaborative projects with investigators both inside and outside of AMP-PD to further accelerate neurological disease research.

Data currently available and estimates of data to be generated with timeline

Much of the AMP-PD research agenda will take advantage of already existing data. The data listed in Table 1 is available now and has been used in several publications^(1,2,3). The PDGSC exome meta-analysis is ongoing and a publication should be ready for submission by early 2017. Storage and analysis of the PDGSC exome data is accomplished using Google Genomics and funding is in place to support data storage and analysis time for the next 8-10 months. Whole genome sequencing (WGS) data listed in Table 2 will be available in early 2017. Storage and analytical costs are part of the AMP-PD budget analysis. Approximately 6,000-10,000 control WGS dataset are or will be available in the first 1-2 years of AMP-PD, with data from several studies including the National Institute of Aging (NIA) NIAGAD project, the National Heart, Lung and Blood Institute (NHLBI) TopMED project, Mayo Clinic 1000 control genome project and the Wellcome Trust. RNA seq, epigenomic, proteomic, robotic imaging data and additional biomarker platform data will be available beginning in the 4th quarter of year 1 and accumulate over the duration of AMP-PD.

(b) (4)

AMP-PD Knowledge Platform Requirements:

The following is a high-level technical description of the components of the proposed AMP-PD Knowledge Platform that could be supported in-kind through Verily, and includes: 1) development of a controlled access AMP-PD Knowledge platform with considerations for data storage and management, standardized pipeline analyses for generation of processed datasets, cloud collaborative project management and where appropriate incorporation of PD3P DMR infrastructure elements to support the AMP-PD Knowledge platform; and 2) development of a AMP-PD public site.

A. Controlled Access AMP-PD Knowledge Platform

Data Storage and management


Table 2 outlines the data storage and computing times required for the various data types generated in AMP-PD Project 1 (Phase 0, Phase 1 and Phase 2) and AMP-PD Project 2. Data types will be collected

against standard form structures developed by the NINDS PDBP data management resource. These form structures are consistent with solutions used across NIH institutes and databases. Raw data will be uploaded to the cloud, processed, and reprocessed, but must be quality controlled prior to submission to the AMP-PD Knowledge Portal. This ensures all data that is managed by AMP-PD Knowledge Portal meets minimum standards of structural validation. Once in the cloud environment, an AMP-PD data coordinating group will check data quality prior to releasing the data for public use. Both raw data and processed data will be stored in the cloud environment. Clinical data currently in the NINDS data management resource and representing PDBP, PPMI, BioFIND and Harvard Biomarker Study cohorts will be moved into the cloud environment. All data sets include Global Unique Identifiers (GUIDs), which enable individual level data analysis. Selected processed datasets generated by standard analysis pipelines will be used to assemble aggregate data that will be used to populate a searchable PD variant database. This database will be accessible on a public facing website and modeled after the University of California San Diego genome browser. To address efficient data storage and associated costs, commonly requested, searched and analyzed data will be promoted for ready use, whereas less common data will be archived to a less expensive storage solution. For long term data access, beyond the period of AMP-PD, all data that is part of AMP-PD will be submitted to the NIH database for Genotypes and Phenotypes (dbGaP) and/or to a NIH Data Commons, if that solution is available within the timeframe of AMP-PD.

Analytical Pipelines

Standard analytical pipelines are essential for coordinating datasets both within and across projects. Since both AMP-PD Projects 1 and 2 will be utilizing shared data-generating platforms for whole genome sequencing, RNA sequencing, epigenomics, proteomics and metabolomics, the best practice for data coordination is to apply common analytical pipelines that would allow for the specific characteristics of the different datatypes. These processed datasets would therefore, for instance, enable analyses within the datatypes generated from AMP-PD Project 1 (which includes iPSC and human tissue derived cell-based data) and AMP-PD Project 2 (which includes data generated from biofluid sample analysis). Common pipeline processes will also enable combined analyses with Project 1 and Project 2 data and will be driven by a DMR-supported authenticated controlled access dataset retrieval service interface. Standard analytical pipelines have been developed for RNA seq (e.g., see the NeuroLINCS example outlined in Figure 1), epigenomics, proteomics (e.g DIA processing and DDA library builds outlined in Figure 1) and metabolomics. These pipelines use standard file formats and open-source tool components like BWA/GATK, Bioconductor, Bioperl, BioJava, Octave, BLAST, Tophat(2), STAR,

(b) (4)



RseQC/cufflinks, IQSEQ, SamTools, iQuant, PRIDE-toolsuite, maxQuant, HTSeq, DESeq2, cuffdiff, HISATZ, FASTQC, Trimmomatic, and others. As illustrated in Figure 2, integrative analysis pipelines are also being developed by the NeuroLINCS project for combining transcriptomic, epigenomic and proteomic datasets. The vision for incorporating data analysis pipelines into the AMP-PD knowledge platform would involve NIH staff working with Verily and pipeline providers to accomplish this task. Overall, the proposed analytical pipelines to be incorporated into the AMP-PD Knowledge platform are ones that have been developed by NIH Common Fund projects or large WGS projects. These pipelines handle processing of WGS, RNA seq, epigenomic, proteomic, robotic image data, metabolomic data, and biomarker platform data. As new analytical techniques are developed NIH staff will work with Verily to bring the related analytical pipelines into the AMP-PD cloud infrastructure.

Figure 1: NeuroLINCS pipeline for RNA Seq Analysis and DIA based proteomic analysis. The NeuroLINCS RNA seq analysis pipeline has been published as a workflow on Galaxy Azure by Microsoft and can be executed using a graphic user interface by biologists.

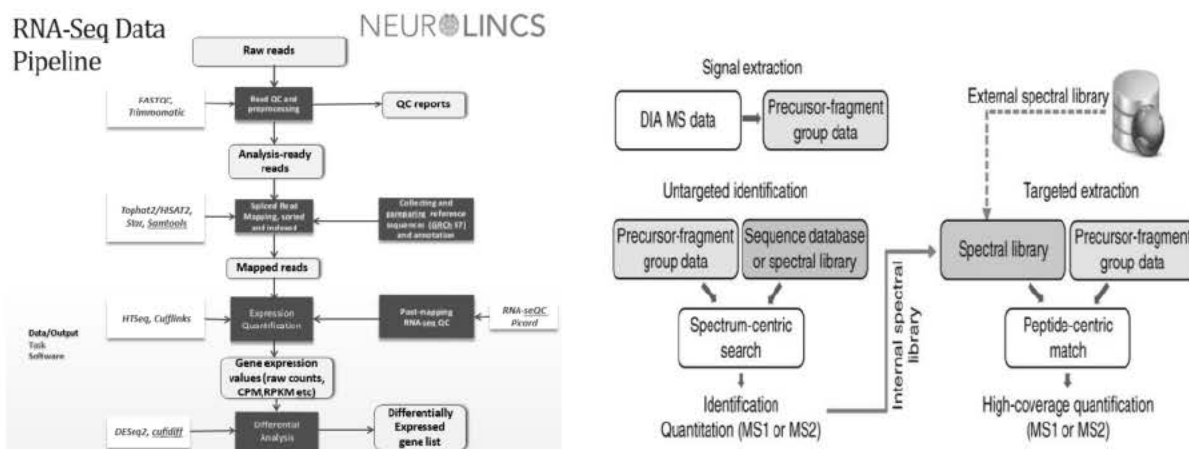
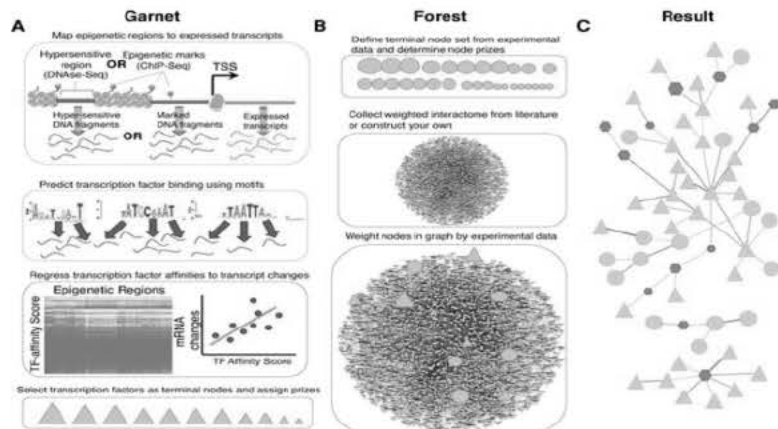


Figure 2: Omics Integrator. The Omics Integrator applies advanced network algorithms to a network of thousands of molecular interactions to find high-confidence, interpretable subnetworks that explain the data. These subnetworks connect changes in gene expression, protein abundance or other global assays to protein that may not have been measured in the screens due to inherent bias or noise in measurements. This approach reveals unannotated molecular pathways that would not be detectable by searching pathway databases. Tuncbag N, Gosline SJ, Kedaigle A, Soltis AR, Gitter A, et al. (2016) Network-Based Interpretation of Diverse High-Throughput Datasets through the Omics Integrator Software Package. PLOS Computational Biology 12(4): e1004879.



Cloud collaborative project management

Support would be provided for a collaborative web-based workbook/project solution that would enable a user to create and share documents that contain live code, equations, visualizations and explanatory text and that enables versioning of data files to track the analytical process. User applications could include data cleaning and transformation, numerical simulation, statistical modeling, machine learning, etc. (e.g. Jupyter, iPython, or a customized system like the Providence solution provided by SAGE).

In terms of the SAGE web-based solution for managing provenance, the concept is to expose a very general data model based on the W3C Prov spec. Central to the design is the principle that users are not required to use a particular execution environment or workflow tool. Instead, provenance can be specified by inserting calls to the synapse web service layer into the user's normal workflows to record activity, and pipelines may be created through simple scripting or by using workflow execution engines.

The provenance system allows users to branch off workflows at any point in prior analyses, while maintaining detailed records of data, code, and environment versions needed to reproduce the work.

Utilization of existing PDBP Data Management System Elements to support AMP-PD infrastructure

The Parkinson's Disease Biomarkers Program Data Management Resource (PDBP DMR) has open source code available for modules that could assist searches within the cloud environment. The data dictionary contains the common data elements and unique data elements used in the form structures. Tools for account management, data uploading, and BD2K indexing are available for incorporation into the AMP-PD data knowledge platform. NINDS will maintain the PDBP DMR during the lifetime of the AMP-PD project to enable continued uploading of clinical data from ongoing Lewy Body Disease biomarker cohort studies. A PDBP DMR infrastructure architect will work with Verily to transition PDBP DMR components/modules to be used in the AMP-PD knowledge platform infrastructure. Components developed and available through the PDBP DMR for integration into the AMP-PD Knowledge platform include:

- a. Dictionary of common Data Elements
- b. Quality control of data uploads against standard form structures
 - i. Data capture, validation and submission tools, form structures for various data types
- c. Study and Protocol Definition
- d. Accounts and Group Management
- e. Dataset Discovery and Record Query Tools
- f. BD2K Indexing, DOI and Publication Management
- g. Public and Protected Sites, Branding & Content
- h. Curation of Harmonized Phenotypes
- i. Tool for Creating Synthetic Cohorts

NINDS DMR infrastructure elements available for integration in the AMP-PD Knowledge Platform



ProFoRMS



GUID



Data Dictionary



Data Repository



Query



Meta Study



Account
Management

Shared Data Dictionary

The PDBP Data Management Resource (DMR) currently has 47 form structures against which data has been collected. Form structures include clinical assessments, genomic (DNA and RNA) data, immunoassay biomarker data, biosample catalog data and imaging data. The data dictionary is made up of 17,681 data elements, of which 11,667 are common data elements. The data dictionary identifies form structures using specific data elements and tracks any change history for the data element. Where

available CDISC standard references are included. This data dictionary also supports the Federal Interagency Traumatic Brain Injury Research Database.

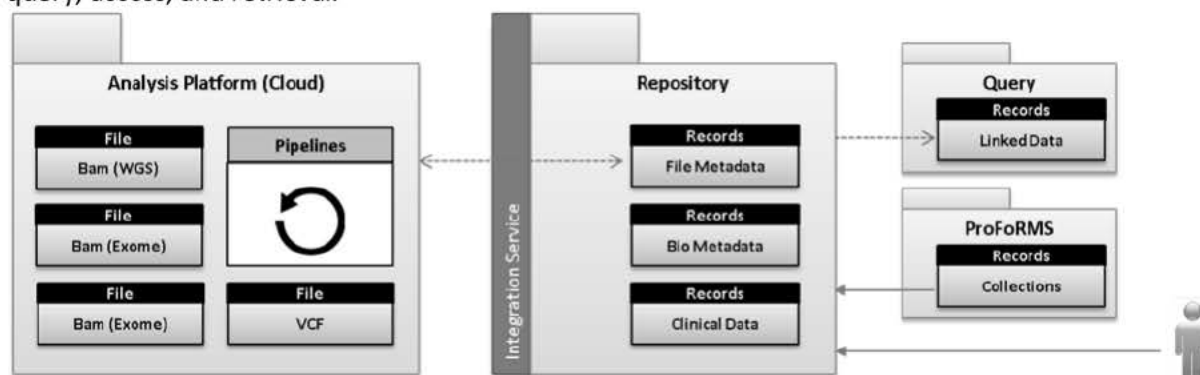
Data Capture, Validation and Submission Tools

Currently the PDBP DMR offers a data validation and upload tool for data that is not captured and validated through the ProFoRMS module. The validation component must be used before any data can be uploaded to the data repository. The validation and submission tools run as a Java Web Start application locally on a user's computer and therefore requires the user to install the Java runtime environment. The validation component verifies that submitted data conforms to the required format and range values defined in the data Dictionary. The tool imports the Data Dictionary and validates the metadata associated with the files identified by the user for submission against the data dictionary. It provides a report of any data discrepancies and warnings. If errors are found, a submission package cannot be created. After successful creation of a submission package, data can be submitted to the system with the upload component. For imaging data, the Medical image processing, analysis and visualization (MIPAV) tool is used. This tool is also run locally on a user's computer as a Java web start application. The MIPAV tool enables users to submit unprocessed brain images in DICOM format and processed images in a variety of formats including DICOM, MINC 1.0 and 2.0, Analyze, NfTI, AFNI and SPM. The MIPAV tool creates files necessary for validation including a compressed image, a JPG file that can be used as a thumbnail to preview the image in the Query tool and a CSV file of the meta-data from the image and represents a form structure that can be queried using the Query tool. The files created for submission must be validated prior to uploading.

Repository Access and Retrieval

AMP-PD data will be stored in the cloud. The current DMR repository provides data management tools to enable access and retrieval without physically moving the data. Users are authenticated through the DMR accounts module, and data rights assigned to AMP-PD users are verified before files may be downloaded or used as input to cloud processes including pipelines on the Analysis Platform. The DMR provides both a data transfer service to upload data to the cloud and pull data from the cloud, as well as a data access service to grant proxy access to AMP-PD data.

The Data Repository provides validation for structured data and file metadata during the submission process. All AMP-PD data must undergo the submission process, where it is validated against structural definitions in the Data Dictionary. Data can be validated in place, through a remote validation client, or through electronic submission through the repository service. Once data is validated and submitted, rights may be assigned to grant access to users, or to groups of users, or made public. All submitted data is linked to entities in the system including User, Study, Dataset, Forms and Elements that facilitate query, access, and retrieval.



File data is stored, processed, and created in the cloud. File metadata submitted to DMR describes physical location information	File metadata is submitted as a DMR dataset. DMR governs access to files by dataset and links metadata to other DMR dataset records	DMR supports data upload and submission via ProFoRMS and client tools. These data are stored in the cloud.
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Discovery and Query Tools

The DMR today supports several types of queryable records-level data: Clinical data and BioSample, Imaging, Genomics and other file metadata. The repository also provides Study definitions and Dataset definitions with required fields sufficient to support discovery both within the system and in the broader community through the BD2K DataMed index. Studies, Datasets, Records, and Files are all identified by a URI that can be used in any application and dereferenced by authenticated users with data rights. These URI's enable linking data with concepts, with other data, with metadata, and across datasets, systems, and discovery indexes.

The DMR currently supports linked data at the record level by subject. This enables users to query clinical data from selected studies and forms, join form data, and discover rich information about subjects across forms. Each set of records for each form in query results can be filtered based on data element values and ranges defined in the Data Dictionary.

Administrative Management of Studies and Datasets in the DMR

All datasets associated with the studies listed in the DMR can be found in the manage datasets list and can be searched by PDBP assigned administrators by keyword, ownership, or dataset status. Dataset status defines the state of the dataset and includes: 1) Private, which is the default status for all datasets until sharing of the dataset is requested; 2) Requested Deletion, a status that can be requested of private or shared datasets by the submitter. Deletion of datasets is a hard delete completed by the PDBP Admin; 3) Requested Sharing, which enables submitters to request the dataset be shared; the PDBP Admin reviews the request; 4) Requested Archive, which enables submitters to request the dataset be archived; the request is reviewed by the PDBP Admin; 5) Shared status, which indicates that the dataset is accessible to all users and cannot be modified or added to; and 6) Archived status, which indicates that the dataset will not show up by default in queries. Results of searches are provided in a tabular format.

As with datasets, all studies are listed in a content page, where users can search by keyword or status and results are shown in a tabular format. In the case of studies the status option includes: requested, public, private, rejected, or all, and defines whether the study can be viewed and data associated with the study shared with users.

B. AMP-PD public site

The public website will support the following functions: 1) information about AMP-PD including description of data and analytical pipelines available, training videos supporting the use of the controlled access database, use case examples of data and analyses available; 2) visualization tools to assist users with data use and management; and 3) a searchable PD variant data base built from aggregate data and modeled after the UCSD genome browser.

PD Variant Database accessible on AMP-PD public site

1. A searchable Parkinson's Variant Database will be developed on a public facing website using aggregate data from WGS analysis with overlay of data from gene expression, protein expression and epigenomic analysis. Analytical capabilities should include data quality assessment and control, preprocessing and scaling, univariate and bivariate statistics, multivariate regression, identification of differentially expressed genes, principle components analysis, unsupervised clustering, allelic association testing, and logistic regression.
2. The public facing website will also include visualization tools to assist users with data management. Visualization capabilities should include volcano plots, heat maps, and Manhattan plots. Interfaces should allow web-based specification of analyses as well as visualization and downloading of results. Tutorials involving sample data sets and analyses to illustrate use of the PD variant database analytical and visualization tools will also be included.

AMP-PD Knowledge Platform Proposal Options

We envision two proposed ways in which Verily could contribute in-kind to supporting the AMP PD knowledge portal.

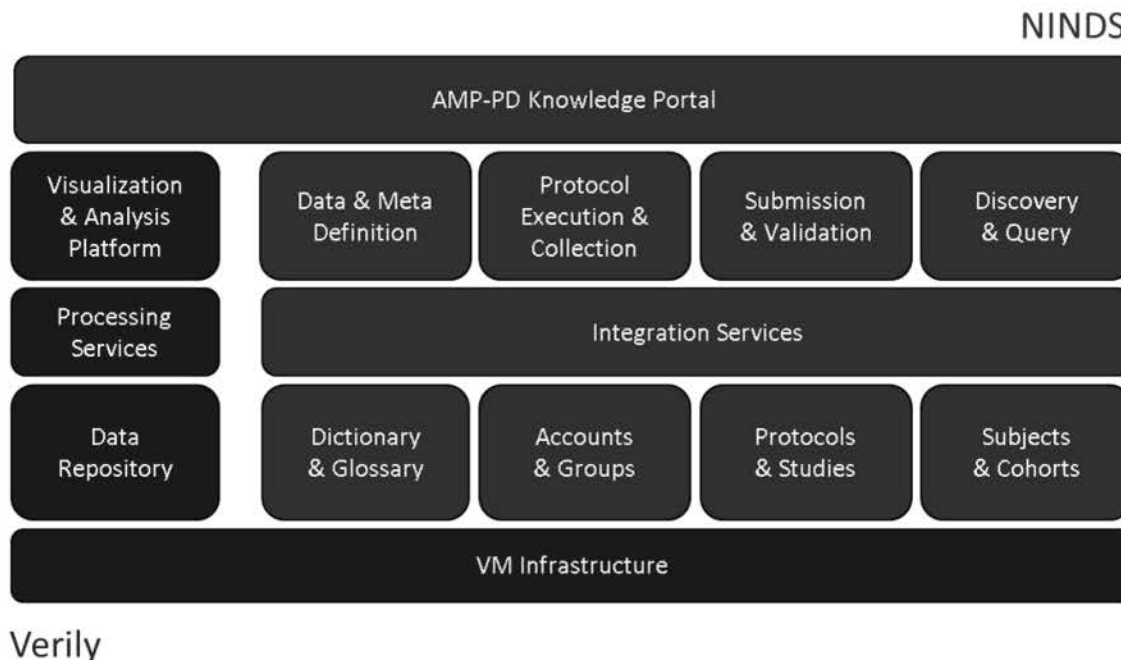
Proposal A: Verily would provide support of data storage, analysis time and infrastructure support for standardized pipeline analysis. In this scenario, once a dataset is quality controlled using a standard form structure and data dictionary, the data submitter will upload the data to the cloud environment and run a standard analysis pipeline for the specific datatype. An AMP-PD data working group will analyze pipeline data for errors prior to posting for broad user access.

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Proposal B: Verily would provide support of data storage, analysis time and infrastructure support for standardized pipeline analysis, integration of relevant infrastructure from PDBD DMR (data dictionary, account management, data capture, validation and upload tools, query tool, harmonized cohort data), public data portal with PD variant database and visualization tools, and cloud collaborative project management.

This option would enable Verily to collaborate in building a technical platform that could be extended beyond PD to accommodate other diseases. We have not estimated commercial pricing for this option.

Figure 3: Outline of Proposal 3 indicating components from NINDS and Verily.



References

- 1) Diagnosis of Parkinson's disease on the basis of clinical and genetic classification: a population-based modelling study. Nalls, MA et al. Lancet Neurol. 2015 Oct;14(10):1002-9. doi: 10.1016/S1474-4422(15)00178-7.
- 2) NeuroX, a fast and efficient genotyping platform for investigation of neurodegenerative diseases. Nalls, MA et al., Neurobiol Aging. 2015 Mar;36(3):1605.e7-12. doi: 10.1016/j.neurobiolaging.2014.07.028.
- 3) Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. Nalls MA et al., Nat Genet. 2014 Sep;46(9):989-93. doi: 10.1038/ng.3043.

From: Wholley, David (FNIH) [T]
Sent: Mon, 20 Nov 2017 14:45:38 +0000
To: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]; Koroshetz, Walter (NIH/NINDS) [E]; Volkow, Nora (NIH/NIDA) [E]; Baker, Rebecca (NIH/OD) [E]; Wolinetz, Carrie (NIH/OD) [E]
Subject: FDA Meeting conflict

All – on this morning's Opioids Biomarker Working Group call Sharon Hertz informed the group that FDA has a meeting on December 11 and 12 to discuss packaging configurations that can reduce risk, and rather publicly suggested that our planned Dec 12-13 meeting would therefore propose a conflict that could be problematic for 'many participants.' Is this the meeting that Nora mentioned in some of our earlier Thursday calls, or something new (she says it is in the FR)? And how should we handle this? We are pretty set for the 12th and 13th and moving the date may be even more problematic for our efforts. I will need to respond to Sharon in any event. Please advise.

Thanks, David

We've moved! Please find our new address below.

David Wholley

Director, Research Partnerships

Foundation for the National Institutes of Health

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fnih.org

11400 Rockville Pike Suite 600 North Bethesda, MD 20852

*Learn more about the FNIH in our **2016 Annual Report**: fnih.org/AnnualReport.*

From: Wholley, David (FNIH) [T]
Sent: Wed, 1 Mar 2017 16:46:51 -0500
To: Lundberg, Jan
Cc: Collins, Francis (NIH/OD) [E]; Tabak, Lawrence (NIH/OD) [E]
Subject: AMP Executive Committee call February 24 notes
Attachments: 2017_02_24_AMP EC teleconference draft final clean.docx

Dear Jan:

I'm sorry you ended up not being able to make our AMP EC call last Friday. So you can stay informed I have attached the minutes we took from the call. Please let me know if you have any questions you'd like me or others to follow up on. I hope you will be able to make our next EC call, scheduled for Friday May 5 from 7:00 – 8:00 AM Eastern U.S. time, and provide your input.

Regards,
David

**Foundation for the National Institutes of Health (FNIH)
Accelerating Medicines Partnership (AMP)
Extended Executive Committee (EEC)
Teleconference Meeting Minutes**

Friday, February 24, 2017

7:00 – 8:00 a.m. EST

Participants

Neil Buckholtz (NIH/NIA), Rosa Canet-Avilés (FNIH), Bob Carter (NIH/NIAMS), Francis Collins (NIH), Francis Cuss (Bristol-Myers Squibb), Michael Decker (AbbVie), Mikael Dolsten (Pfizer), Ellen Gadbois (NIH), Richard Hodes (NIH/NIA), Marty Hodge (Pfizer), Steve Hoffmann (FNIH), Stephen Katz (NIH/NIAMS), Walter Koroshetz (NIH/NINDS), Allison Lea (NIH), Joseph Menetski (FNIH), Dina Paltoo (NIH), Griffin Rodgers (NIH/NIDDK), Laurie Ryan (NIH/NIA), Susana Serrate-Sztejn (NIH/NIAMS), Philip Smith (NIH/NIDDK), Nicole Spear (FNIH), Margaret Sutherland (NIH/NINDS), Larry Tabak (NIH), Melissa Thomas (Lilly), David Wholley (FNIH)

(b) (4), (b) (5)

From: Wholley, David (FNIH) [T]
Sent: Fri, 23 Jun 2017 18:33:31 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: AMP Extended EC 6-30-2017 v2 - DRAFT 6-23.pptx
Attachments: AMP Extended EC 6-30-2017 v2 - DRAFT 6-23.pptx

Hi Francis –

Here are the draft slides for the Extended EC teleconference next Friday June 30. If you have time to take a look, please let me know if you have any comments or suggestions. Unless you disagree I would plan to send the complete text document with the Cardon/Vallance proposal and the three disease area responses along with these as a pre-read, so would plan to send out no later than Tuesday. Thanks,
David

Accelerating Medicines Partnership Extended Executive Committee Update #6

30 June 2017

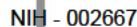


NIH - 002

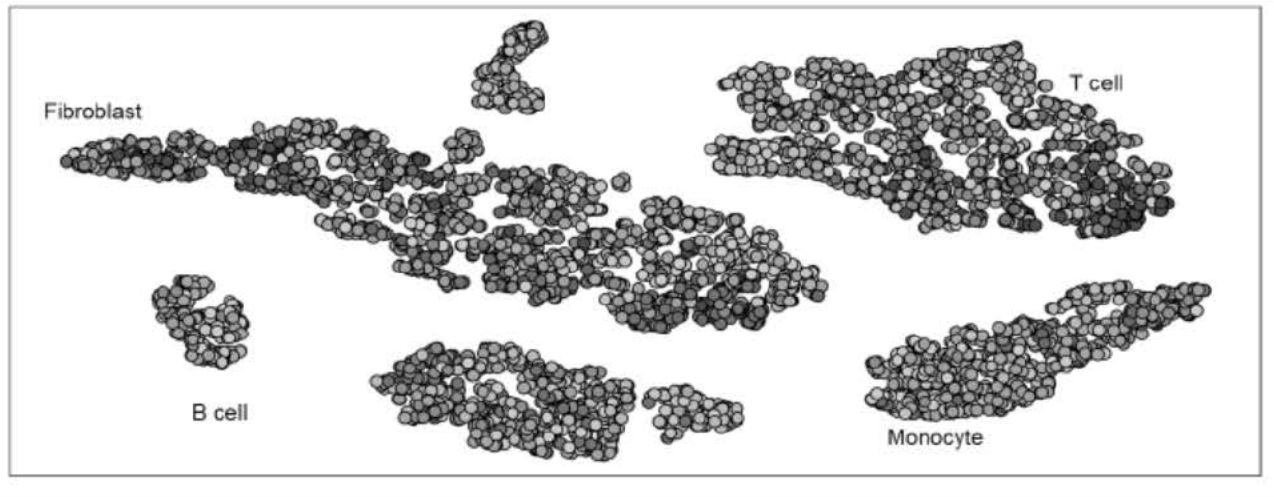


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(b) (4)



Accelerating Carter, NIAN



FNIH

Foundation for the
National Institutes of Health

NIH - 002678



Accelerating Medicines Partnership Alzheimer's Disease

Laurie Ryan, NIA

(b) (4)



NIH - 002689



Accelerating Medicines Partnership Parkinson's Disease Program Development Marg Sutherland, NINDS



FNIH

Foundation for the
National Institutes of Health

NIH - 002699



Extended Executive Committee

- **Next Meeting:AMP Extended Executive Committee:
December 15, 2017 from 7:00am – 8:30 am Eastern
US Time**

From: Wholley, David (FNIH) [T]
Sent: Mon, 11 Dec 2017 21:25:16 +0000
To: Collins, Francis (NIH/OD) [E]
Cc: Gadbois, Ellen (NIH/OD) [E]; Singh, Jyoti (NIH/OD) [E]; Melencio, Cheryl (FNIH) [T]
Subject: AMP Extended EC 12-15-2017 2nd DRAFT.pptx
Attachments: AMP Extended EC 12-15-2017 2nd DRAFT.pptx

Hi Francis – As requested, here is the second pass at the slides for the AMP EEC this Friday. We've done our best to work with the co-chairs to prune and improve the slides per your feedback on last week's pre-call. Let us know what you think, including where you think there are any additional opportunities for condensing this. Thanks, David

Accelerating Medicines Partnership Extended Executive Committee Update #7

15 December 2017



NIH - 002



Accelerating Medicines Partnership Type 2 Diabetes

Phil Smith, NIDDK

(b) (4)



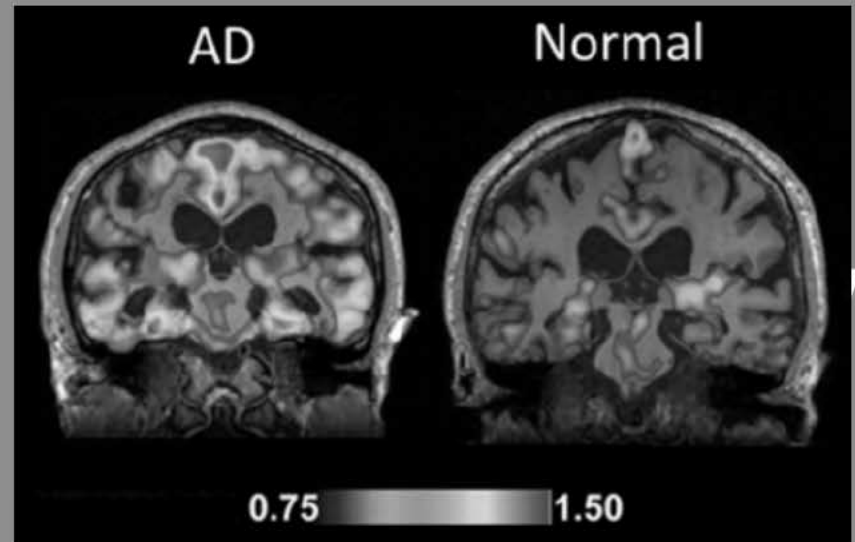


FNIH

NIH - 002727



Accelerating Medicines Disease Laurie Ryan,



FNIH

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National Institutes of Health

NIH - 002748



Accelerating Medicines Partnership Parkinson's Disease Program Development

(b) (4)

(b) (4) Marg Sutherland, NINDS



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National Institutes of Health

NIH - 002763



- **Next Meeting:AMP Extended Executive Committee:
June 29**

Backup Slides

From: Wholley, David (FNIH) [T]
Sent: Sun, 11 Jun 2017 20:50:12 -0400
To: Collins, Francis (NIH/OD) [E]
Subject: AMP Extended EC attendee slide.pptx
Attachments: AMP Extended EC attendee slide.pptx

Hi Francis, just thought you'd want to know we have pretty good attendance projected for the Extended EC on June 30 – except for Jan Lundberg, (b) (6), and Jim Sullivan of AbbVie, who had been tentative but will likely not be able to attend. I can ask both of them to appoint alternates if you wish. FYI, Elias Z. just responded positively on Thursday. Thanks, David

Today's meeting participants

Industry participants

	• Michael Decker
	• Spyros Artavanis-Tsakonas
	• Lon Cardon
	• Bill Hait (not attending) Mark Erion Paul Stoffels James Sullivan
	• Jan Lundberg (not attending) Melissa Thomas
	• Joseph Miletich
	• Mikael Dolsten Marty Hodge
	• Elias Zerhouni Gary Nabel
	• Salvatore Alesci

Government participants

	National Institutes of Health <i>Turning Discovery Into Health</i>	• Francis Collins Ellen Gadbois Allison Lea Dina Paltoo Larry Tabak
	National Institute on Aging	• Richard Hodes Neil Buckholtz Laurie Ryan
	National Institute of Allergy and Infectious Diseases	• Dan Rotrosen Ellen Goldmuntz
	National Institute of Arthritis and Musculoskeletal and Skin Diseases	• Bob Carter Stephen Katz
	National Institute of Diabetes and Digestive and Kidney Diseases	• Griffin Rodgers Philip Smith
	National Institute of Neurological Disorders and Stroke	• Walter Koroshetz Margaret Sutherland
		• Janet Woodcock

Academic Participants



NIH - 002784

- Richard Lifton

Non-profit participants

	alzheimer's association®	• Maria Carillo James Hendrix
	Alzheimer's Drug Discovery Foundation	• Howard Fillit
	Genetic Alliance	• Sharon Terry (not attending)
	Arthritis Foundation™	• Guy Eakin Amanda Niskar Debra Lappin
	JDRF IMPROVING LIVES. CURING TYPE 1 DIABETES.	• Marlon Pragnell
	LUPUS FOUNDATION OF AMERICA	• Leslie Hanrahan
	LUPUS RESEARCH ALLIANCE	• Mary Collins
	PRMA RESEARCH - PROGRESS - HOPE	• William Chin (Not attending)
	Rheumatology Research Foundation Advancing Treatment Finding Cures	• Eryn Marchiolo Teresa Tarrant (not attending)

Program Management

- David Wholley
Rosa Canet-Aviles
Steve Hoffmann
Lilit Vardanian



From: Wholley, David (FNIH) [T]
Sent: Tue, 11 Apr 2017 11:27:20 -0400
To: Collins, Francis (NIH/OD) [E]
Cc: Koroshetz, Walter (NIH/NINDS) [E]; Sutherland, Margaret (NIH/NINDS) [E]; Canet-Aviles, Rosa (FNIH) [T]; Baker, Rebecca (NIH/OD) [E]; Lea, Allison (NIH/OD) [E]; Gadbois, Ellen (NIH/OD) [E]
Subject: AMP Parkinson's Disease update
Attachments: AMP PD Proposal Update 04_2017.pdf, AMP PD overview April 2017with AMP.pptx, AMP PD Integrated_Proposal_Final.pdf

Francis, please see below suggested note. I included a few upfront slides on AMP in the powerpoint deck in case anyone needs context, but you can also delete these if you wish and start at current slide #7. I am checking in with Todd on where conversations stand with Sergey Brin to make sure have context for a potential approach and will be back to you. (b) (6)
so have asked to include Rosa as a contact as well. Thanks, David

Dear HEVER members:

It was a pleasure meeting with you all this past weekend. As I noted in my talk on Saturday, we are very pleased to be readying the launch of a new AMP initiative, in Parkinson's disease. The current projected budget for AMP-PD over five years totals (b) (4) to be contributed by NIH, and commitments (b) (4) (through the Foundation for the NIH) from each of five private sector partners: GSK, the Michael J. Fox Foundation, Pfizer, Sanofi, and Verily. As I mentioned, by agreement among the partners AMP-PD will initially focus on developing biomarkers to support better clinical trial designs in PD.

In the event that some of your companies may be interested in joining the current partners in AMP-PD, I've attached an executive summary of where the partnership stands, along with a slide deck and the original "white paper" research proposal for those who may want more detail. FNIH is planning a face to face meeting of all the partners on June 1-2 in the DC area to refine the white paper into a detailed research plan with final budgets, timelines, logistics and milestones. There is still some time to consider joining AMP-PD, therefore, but FNIH has asked that if you have any renewed interest in doing so that you at least signal that to David Wholley or Rosa Canet-Aviles (copied) by May 1.

Regards,
Francis

Accelerating Medicines Partnership Parkinson's Disease Initiative Update 4/10/2017

The Accelerating Medicine Partnership (AMP) in Parkinson's Disease (PD) is a proposed partnership between the National Institutes of Health, industry partners and non-government organizations with the goals of executing innovative research that advances the identification and validation of new therapeutic targets for drug development and biomarkers that will support better clinical trial designs in PD.

In August 2016 an AMP-PD Technical Working Group was convened and tasked with drafting a white paper that represented the first stage of a consensus research plan on the key challenges the initiative should address. The original plan contained in the white paper considered a broader scope that included two projects; 1) Targets and Assays, which would identify and validate putative new therapeutic targets for PD based on genetics, and 2) Clinical Biomarkers to enable Proof-of-Concept (POC) Trials, which would focus on the validation of clinical biomarkers to be used in Phase 2 POC trials. **After thorough review by all partners, a decision was made to move forward with Project 2 only for now.**

As stated in the AMP PD white paper, Project 2 takes advantage of already existing clinically phenotyped, longitudinal, genetically characterized PD cohorts with extensive, state-of-the-art linked longitudinal biobanks (*PPMI, PDBP, Harvard Biomarkers Study, PARS, and others*). The proposed assays encompass deep molecular characterization, neuroimaging, multimodal imaging, and profiling of PD patients. The proposal includes a plan for open data access and sharing to dissect new targets, disease subtypes, and markers that track and predict progression. Additionally, AMP PD is designed with a key element to provide an interface for data access and analysis for AMP PD investigators and the larger research community: the AMP-PD Knowledge Platform. As further detailed in the white paper AMP PD is designed as a five-year effort, with launch currently projected for 3Q 2017.

(b) (4)

(b) (4) Details on

these are described in the white paper beginning on page 23.

FNIH has currently raised (b) (4) for AMP PD, committed over 5 years from six AMP PD partners: NINDS, GSK, MJFF, Pfizer, Sanofi and Verily. (b) (4), and \$10 million represents new NIH grants. This level of funding will enable a number of the already identified buy-ups to be funded. The selection of which buy-ups to prioritize, as well as other detailed aspects of the final research plan (e.g., exact project logistics and budget allocations, start dates, timelines, and milestones) will be decided by representatives of the committed private sector partners and NIH in a face to face meeting to be convened by FNIH on June 1st and 2nd of 2017 in Bethesda, MD.

Accelerating Medicines Partnership Parkinson's Disease



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AMP: Accelerating Medicines Partnership

- Major public-private partnership involving NIH and ten pharmaceutical companies
Aims to distinguish targets of disease most likely to respond to new therapies
Partners have developed research plans; are sharing costs, expertise, resources
NIH and private sector have so far invested ~\$187M over five years on projects in three major disease areas

AMP research topics (May 2016)

Disease area	Research plan topics	Deliverables and approach
Alzheimer's disease	Exploratory biomarker validation in clinical trials and network analysis on human tissue	<ul style="list-style-type: none"> • Embed tau imaging and exploratory liquid biomarkers in NIH-funded clinical trials to develop biomarkers of disease progression and surrogate endpoints • Conduct network analysis in human brain samples to identify genetic nodes & networks linked to AD to support target identification & validation
Type 2 Diabetes	Sequencing & phenotyping of targets of interest and a tool to enable easy interrogation of all available data	<ul style="list-style-type: none"> • Create a knowledge portal containing comprehensive T2DM (& diabetic complications) genotype/phenotype data sets – apply informatics to identify predictors of risk and potential drug targets • Conduct targeted sequencing/genotyping of high priority targets of interest (as defined by industry) and phenotyping on patients with high priority variants
RA, SLE & related autoimmune diseases	Immune module deconstruction with blood/tissue and cross-disease comparisons	<ul style="list-style-type: none"> • Conduct extensive profiling of key immune modules in highly refined subsets of relevant cells in informative cohorts to establish pathway/network maps of RA & SLE • Identify high priority targets identified from pathway analysis to be validated via RNAi. Make all data available in a knowledge portal - Informative cohorts include: Early RA, Established RA (responder/non-responder), Lupus Nephritis, Skin Lupus

Current AMP participation by disease area

Alzheimer's disease

Type 2 Diabetes

RA, SLE & related

Industry members

abbvie

biogen idec

 GlaxoSmithKline

Lilly

Johnson & Johnson

Lilly

 MERCK

Pfizer

SANOFI 

abbvie

 Bristol-Myers Squibb

 MERCK


Pfizer

SANOFI 

Takeda


Government members

 National Institute on Aging

 National Institute of Neurological Disorders and Stroke



 National Institute of Diabetes and Digestive and Kidney Diseases

 National Institute of Arthritis and Musculoskeletal and Skin Diseases

 National Institute of Allergy and Infectious Diseases

 PRMA
RESEARCH • PROGRESS • HOPE

Non-profit members



Alzheimer's
Drug Discovery
Foundation

alzheimer's  association

GEOFFREY BEENE

USagainst
Alzheimer's

LUPUS
FOUNDATION OF AMERICA

 Lupus
Research
Institute



Rhina Research Foundation
Advancing Treatment | Finding Cures



Alliance for Lupus Research
PREVENT. TREAT. CURE.



**American
Diabetes
Association.**

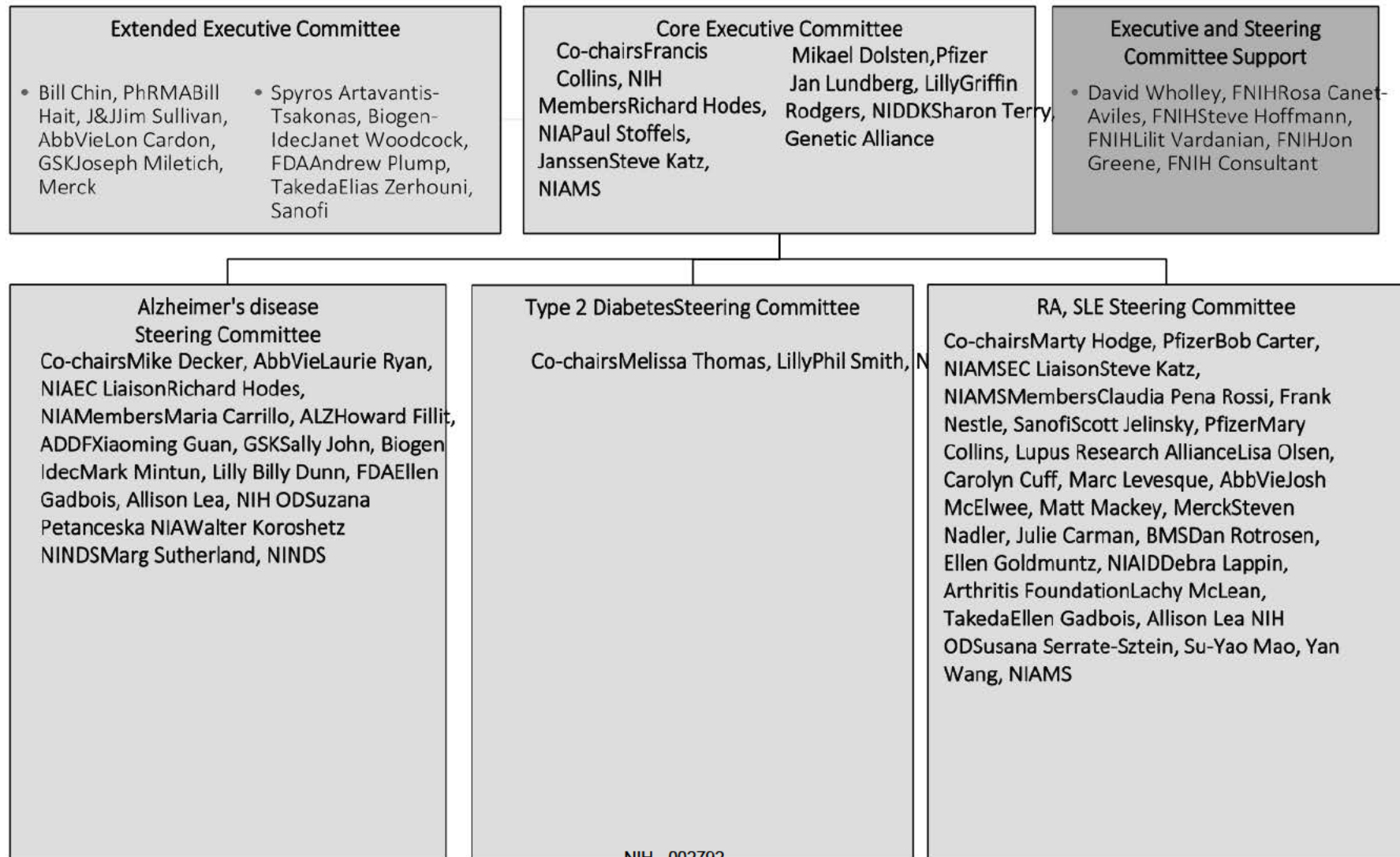
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AMP – IP & data sharing

- Research supported by AMP will be precompetitive Data will be shared broadly and quickly; AMP participants have access to data during assessment of data quality (up to 6 months) No pre-emptive patenting to ensure broadest possible opportunity for commercialization

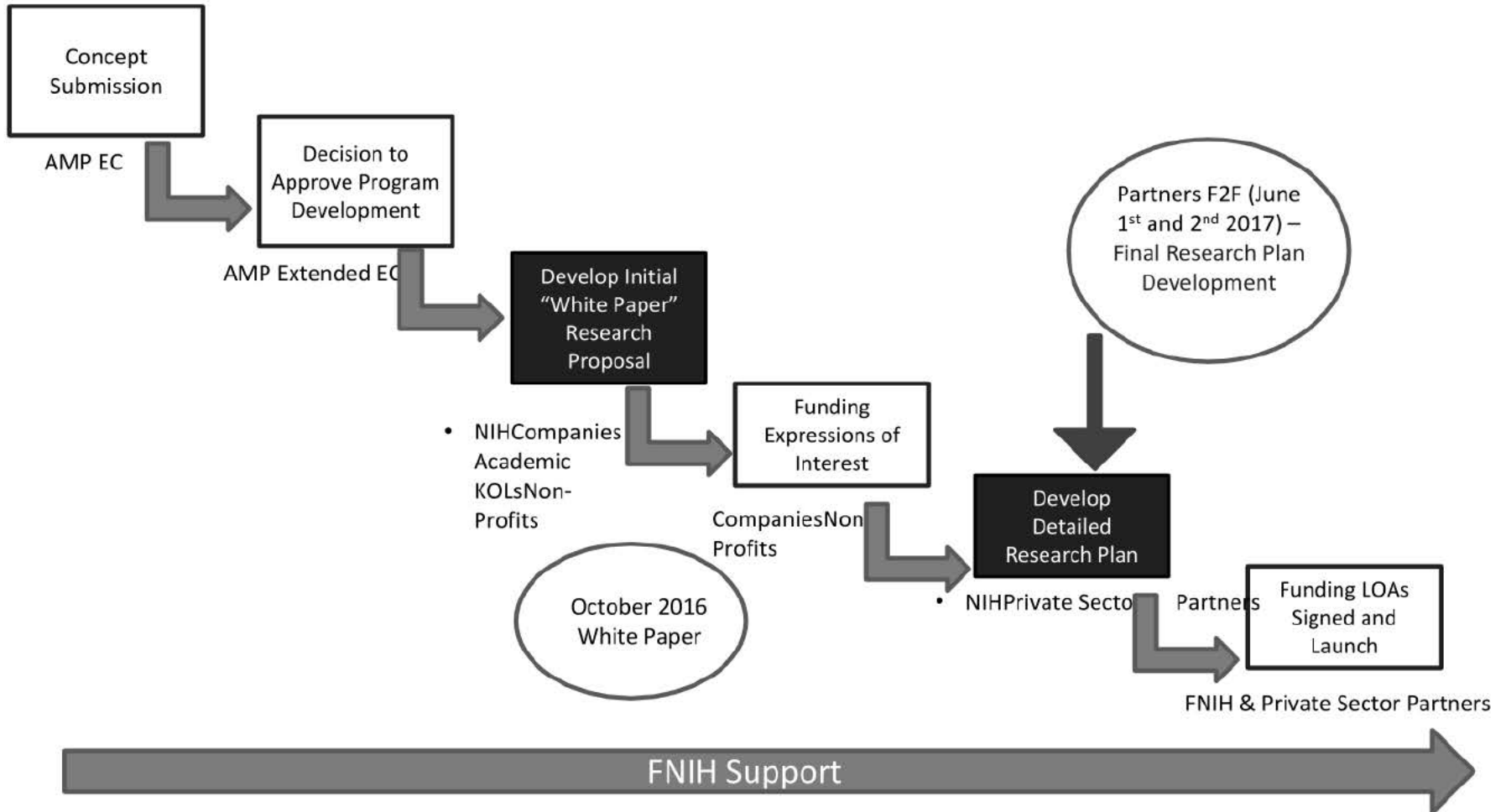


AMP Governance and Membership



NIH - 002792

AMP PD Program Development



Current team structure & membership for AMP-PD

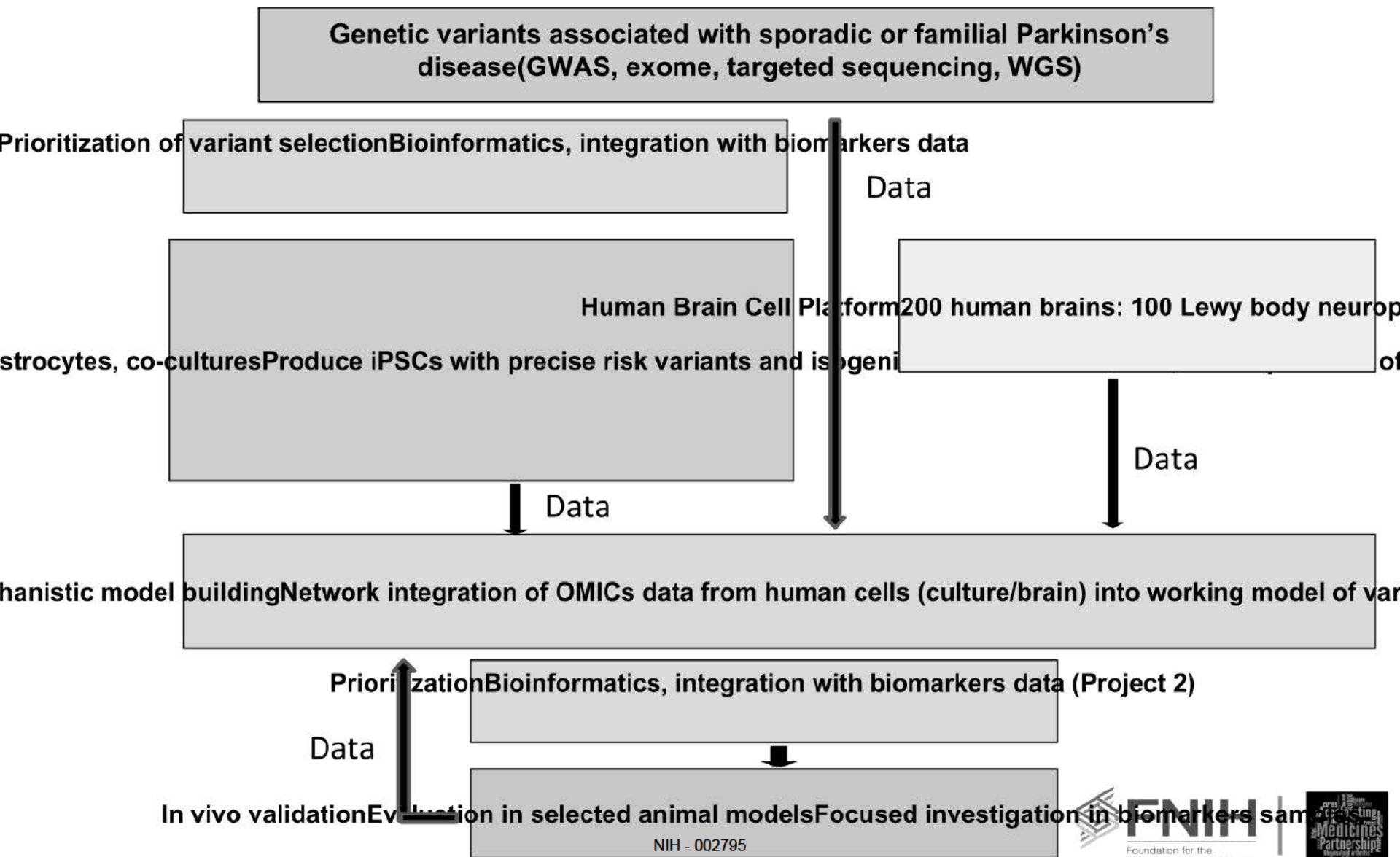
Parkinson's Disease

Co-chairs To be nominated during the Face to Face (June 1 and 2, 2017)
EC Liaison Walter Koroshetz (NIH/NINDS)
Members Rita Balice-Gordon (Sanofi) Peter Bergethon (Pfizer) Tanya Fisher (Sanofi) Mark Frasier (Michael J. Fox Foundation) Ellen Gadbois (NIH/OD) Allison Lea (NIH/OD) Min Li (GSK) Anna Naito (Michael J. Fox Foundation) Todd Sherer (Michael J. Fox Foundation) Marg Sutherland (NIH/NINDS) William Marks (Verily) David Glazer (Verily) Chris Leptak (FDA) (+ other FDA pending)

NIH - 002794



Original plan: AMP-PD Project 1 (Targets and Assays)



Original plan: AMP-PD Project 2 (Clinical Biomarkers)

Existing Longitudinal Cohorts: MJFF PPMI, NINDS PDBP, Harvard Biomarker Study (overall > 3,000 PD cases and 1,000 controls) Biosamples available: 3313 CSF samples, 15,430 RNA samples, 10,392 plasma samples, 4,000 DNA samples, PBMCs

Platforms

RNA
Seq(blood
based)

Proteomics
unbiased
and
targeted MS
CSF, plasma

Metabolomics
Plasma

Lipidomics
Plasma

Imaging
and clinical
data

Standardized Data collection including meta data standards and QC



and processed platform data to AMP-PD Knowledge Platform Inform biosample analysis from p
Project #1

Cohorts and Tissues

- Availability of established cohorts with well-characterized patient populations
Wide range of tissue types which can be assayed on various – omics platforms

Cohort	DNA	RNA	CSF	Whole blood	Blood Pellet	Plasma	Serum	Urine	Saliva	Cell Lines	PBMCs
PPMI	✓	✓	✓	✓		✓	✓	✓		✓	✓
BioFIND	✓	✓	✓		✓	✓		✓	✓		
PDBP	✓	✓	✓	✓		✓	✓				✓
LCC		✓	✓	✓		✓	✓	✓			
24-Hour Biofluid Sampling			✓	✓		✓	✓				
DATATOP	✓		✓				✓	✓			
Interventional Trials (SURE-PD, FS-Zone)		✓	✓	✓		✓		✓			
LRRK2 Biobanking Initiative								✓			✓
Harvard Biomarker Study	✓	✓	✓	✓	✓	✓	✓			✓	✓
Kassel Repository	✓	✓	✓	✓		✓	✓	✓	✓		

AMP- PD Timeline

Tasks		Q1Y17			Q2Y17			Q3Y17			Q4Y17			2018	2019	2020	2021	2022
		Jan	Feb	Mar	Apr	May	June	July	Aug	Sept	Oct	Nov	Dec					
1	Final Research Plan Development																	
2	NIH RFA Development and Awards																	
3	Letters of Agreement with Partners																	
4	Contracts																	
5	Project Launch																	
6	Biomarker Analysis																	
7	AMP-PD Knowledge Platform																	

 Projected
 Completed

ACCELERATING MEDICINES PARTNERSHIP – PARKINSON’S DISEASE

The Accelerated Medicines Partnership (AMP) is an innovative precompetitive collaboration among the National Institutes of Health (NIH), 10 biopharmaceutical companies, and several nonprofit organizations to transform the current model for developing new diagnostics and treatments. AMP harnesses the collective capabilities, scale, and resources of its partners to understand complex, heterogeneous diseases more fully in order to better identify and validate novel, clinically relevant therapeutic targets and accelerate the process of bringing new medicines to patients. AMP is an ‘umbrella’ partnership with specific initial programs launched already in three major disease areas: Alzheimer’s disease, Type 2 diabetes, and the autoimmune disorders of rheumatoid arthritis and systemic lupus erythematosus. The research in AMP is funded approximately 50/50 by NIH and private sector partners, and is managed by the Foundation for NIH.

The suggestion for a Parkinson’s disease (PD) initiative was originally catalyzed by a proposal submitted to the AMP Executive Committee (EC) in October of 2015. Having received firm expressions of interest from GSK, Lilly, Pfizer, Merck, the Michael J. Fox Foundation, and the National Institute of Neurological Disorders and Stroke (NINDS) in proceeding to build an AMP-PD initiative, the AMP-PD Technical Working Group (*) was created and tasked with drafting the present white paper that represents the first stage of a consensus research plan on the key challenges the initiative should address. Once funding partners have been identified, a modified Working Group will be convened to develop the final research plan, with final committed goals, budgets, and milestones.

(*) AMP-PD Technical Working Group

Co-chairs

- David Stone (Merck); Industry co-chair
- Clemens Scherzer (Harvard); Academic co-chair

AMP EC Liaison

- Walter Koroshetz (NIH/NINDS)

Members

- | | |
|--|--|
| • Peter Bergethon (Pfizer) | • Ameet Parekh (FDA/CDER) |
| • Ted Dawson (JHU) | • Gerald David Podskalny (FDA/CDER) |
| • Steve Finkbeiner (UCSF/Gladstone) | • Todd Sherer (Michael J. Fox Foundation) |
| • Mark Frasier (Michael J. Fox Foundation) | • Andrew Siderowf (Lilly) |
| • Wade Harper (Harvard) | • U. Shivraj Sohur (Pfizer) |
| • Min Li (GSK) | • Marg Sutherland (NIH/NINDS) |
| • Allison Lea (NIH/OD) | • David Vaillancourt (University of Florida) |
| • Ken Marek (INDD) | |

OVERVIEW

No cures exist, but the number of Parkinson’s patients is expected to nearly double to 9.3 million in 2030. Because of aging populations, PD poses an increasing threat to public health with annual costs estimated at \$10.8 billion in the U.S. alone. Complex, genetic diseases such as PD are thought to be caused by combinatorial effects of environmental, epigenetic, and genetic contributions. Progressive loss of dopamine neurons in the substantia nigra pars compacta (SN) and an increasing burden of α -synuclein-positive neuronal inclusions (the so called Lewy bodies) are hallmarks of PD, but the molecular events that cause dopaminergic neurons to die and Lewy bodies to form are not known.

Despite 15 neuroprotection trials involving 4,087 participants and several hundreds of millions of dollars spent, no disease-modifying drugs are approved for PD. Without bold discoveries and transformative public-private partnerships there will be no breakthroughs.

CHALLENGES: MOVING FROM GENETICS TO UNDERSTANDING OF DISEASE PATHOPHYSIOLOGY

After surveying multiple pharmaceutical companies, in addition to academic and non-profit organizations, it is clear that target identification and validation are defined differently in different organizations. However, one common theme that has emerged is that if we are to consider a gene/target “valid” and worth follow-up and the expenditure necessary for the identification of chemical matter for pharmacological manipulation, we must have demonstrated *causal human biology*. While the best-case scenario is obviously to have clinical proof of concept (POC), this is not an option for PD disease-modifying candidates (with no effective treatments on the market). The consensus appears to be that in the absence of clinical POC, our best predictors of causal human biology are strong *genetic evidence*, and *known disease pathology*.

There are multiple challenges around moving from a genetic target to a candidate therapeutic, but a number of AMP-PD members have pointed out that the central problem is moving from the causal genetic variant to an understanding of how that variant affects the pathophysiology of PD. For example, a large number of highly significant GWAS peaks or “hits” have been identified. However, for many of these PD-associated signals, many genes are present under the peak, and it is unclear which one or ones are driving the association. Even if only one gene is present, it is not immediately clear in most cases which variant or variants are associated with increased PD risk. Most importantly, the *causal* variant underlying each of these association signals and its functional consequences in vulnerable dopamine neurons are *unknown*. This question is critical, as the strategy for drugging a dominant gain-of-function mutation is different than for a loss-of-function or deletion variant; indeed, pharmacologically driving the activity of a risk gene in the wrong direction may be worse than doing nothing, and could quite feasibly worsen the condition or increase the rate of disease progression. Complicating matters further, most GWAS-derived variants are in noncoding regions, either in introns or intergenic regions without proven link to a druggable target gene. In some instances, such variants might alter enhancers or repressor elements and regulate nearby protein-coding genes; in other instances, they might regulate more distant genes (e.g., variants in distant enhancers can loop to promoters of target genes through three-dimensional chromosomal looping) or noncoding RNAs. Even when the disease-associated variants are well established (as for LRRK2 and GBA), the lack of understanding of how they drive disease risk and phenotype hinders pharmacological programs, as readouts to determine if candidate therapeutics are driving activity in the correct direction are a “best guess.”

CHALLENGES: HOW TO BEST ENABLE POC TRIALS FOR CANDIDATE THERAPEUTICS

The second major theme coming from the majority of AMP-PD members is the need for validated biomarkers which can be used in phase 2 POC trials to determine if candidate therapeutics are having an effect on the critical physiology of PD. While the final and most important readout for determination of success, registration, and ultimate patient benefit will be the effect on the clinical phenotype, intermediate biomarkers will be critical for early monitoring of compound activity on pathophysiology. The importance of these clinical biomarkers has not been ignored by the field, with multiple longitudinal studies – the NINDS Parkinson's Disease Biomarkers Program (PDBP), Parkinson's Progression Markers Initiative (PPMI), Harvard Biomarkers Study (HBS), Parkinson's Associated Risk Study (PARS), etc. – currently underway to identify imaging, molecular and clinical readouts.

Key questions will need to be addressed concerning candidate biomarkers: Is the biomarker informative for a disease mechanism? How does the marker change over the course of PD? Does the marker inform on target engagement? Is the marker useful for patient stratification? Can the marker be used to identify an early-stage or prodromal patient population? Validated markers meeting one or more of these criteria will be useful in de-risking disease-modification clinical POC trials.

PROPOSAL 1: TARGETS AND ASSAYS

From proven genetic variants to understanding their functional effects in the pathobiology of human neurons and glia --- in culture, in human brains, and through *in vivo* model systems

Executive Summary. The goal of this component of the AMP-PD program is to identify and substantiate putative therapeutic targets for PD by functionally evaluating them in a cell-type-specific manner in human neurons and glia --- in iPSCs-derived cells *and* in human brain cells, *and*, selectively, through *in vivo* model systems. Putative targets will be nominated directly from an up-to-date integrative analysis of large-scale, replicated human genetic data (from available and ongoing meta-GWAS, exome, targeted sequencing, whole genome sequencing studies), data from the *Human Functional Evaluation* and *Human Brain Cells Platforms* (AMP-PD Project 1), and data from the *Clinical Biomarkers Platform* (AMP-PD Project 2).

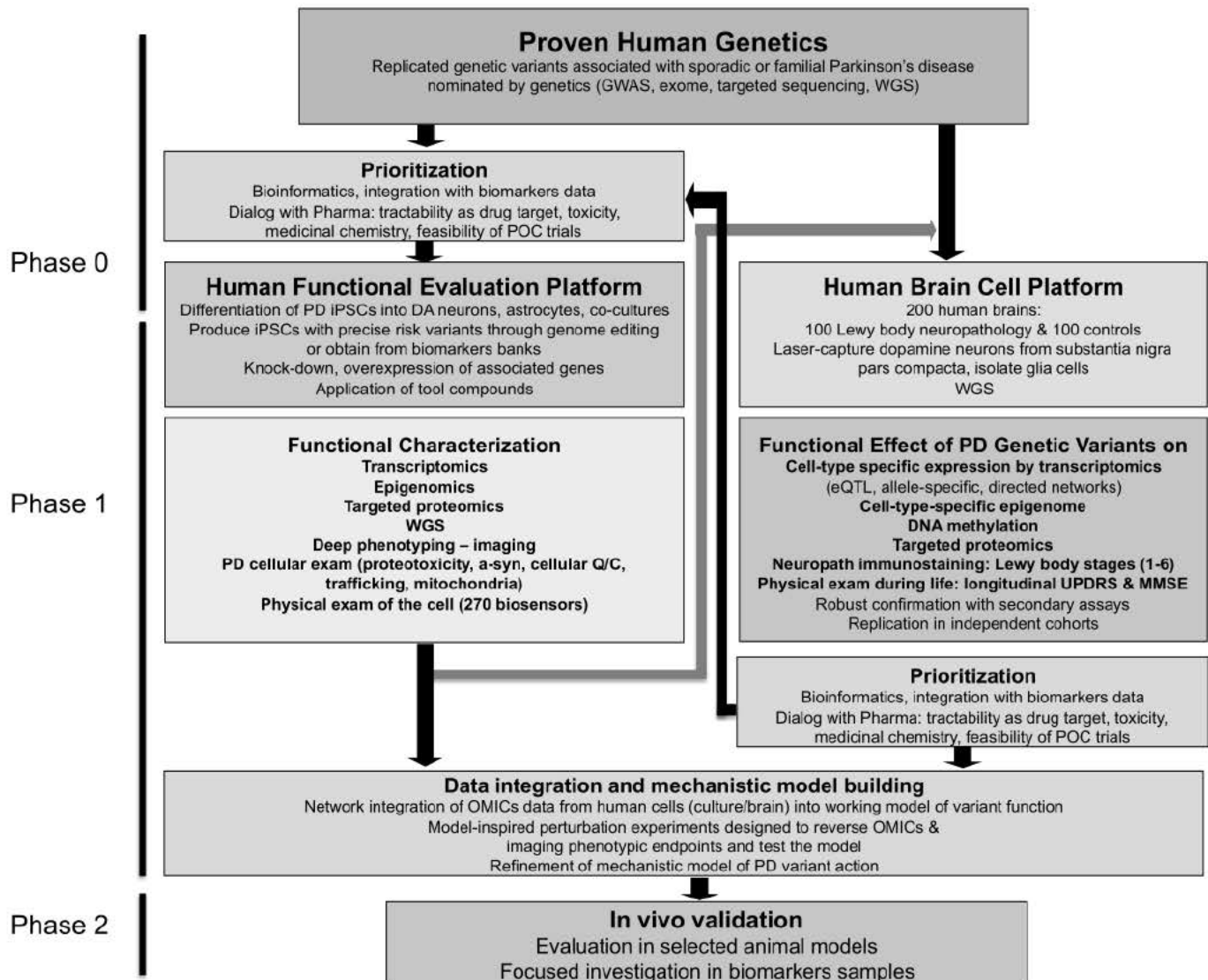


Fig. 1. Overview of AMP-PD Proposal 1

The functional consequences of proven genetic variants for PD will be decoded in human *cultured* and *brain* dopamine neurons and glia relevant to PD through massively parallel, multi-scale OMICS and pathophysiology analysis. Parallel OMICS analyses in life and postmortem human cells, as well as in biofluids of biomarkers study patients (AMP-PD Project 2), will be performed at the level of the genome, transcriptome, epigenome, and targeted proteins using identical platforms and pipelines. On the *Human Functional Evaluation Platform*, genetic and chemical perturbations in iPSC-derived cells will mechanistically and dynamically clarify the effect of prioritized variants on single cells with robotic, high-throughput deep molecular imaging, a PD cellular exam (probing the essential PD-

associated processes of α -synuclein uptake, spread, and aggregation; cellular quality control pathways; and mitochondrial phenotypes), and a general “cellular physical exam” of 270 biosensors. On the *Human Brain Cell Platform*, the as yet unknown, putative causal common variant(s) underlying each of the twenty-four association peaks identified by GWAS of tens of thousands of cases and controls will be delineated using gene expression Quantitative Trait Locus analysis, protein expression Quantitative Trait Locus analyses, and chromatin state maps. The associated *cis*-regulated genes and regulated networks (integrating common, low, rare frequency variants and familial PD genes) will be deciphered precisely where the disease is preferentially active --- in PD-vulnerable dopamine neurons laser-captured from the substantia nigra pars compacta of a total of 200 neuropathologically and clinically characterized individuals with subclinical PD, clinically manifest PD, and controls (many with available longitudinal movement and memory exams). Glia cells will be similarly isolated and analyzed. Moreover, the highly complementary *Biomarkers Platform* (AMP-PD Project 2) will characterize the function of PD-associated variants on the transcriptome, epigenome, and on targeted proteins in biofluids of patients longitudinally tracked with neuroimaging and clinical phenotyping. Dialog with pharma partners at key decision points will assess a target’s druggability, availability of tool compounds or late stage clinical assets, anticipated side effect and toxicology profiles, potential for proof-of-concept enabling biomarkers, and the feasibility of a clinical trial around a target. Finally, *in vivo* non-human PD models, despite their limitations, will be used to complement the *in vitro* mechanistic evaluation of the highest priority PD-associated genetic variants and genes.

Integration of massively parallel data from human genetics, human brain cells, clinical biomarkers studies, and human cellular mechanisms will delineate the multi-dimensional structure of the molecular networks regulated by PD variants and identify the most relevant and druggable drivers and companion biomarkers for each network. The deliverables to pharma from this project will be a series of potential targets directly linked to PD through human genetic and functional studies, and mechanistically elucidated by deep phenotyping with OMICS and imaging, and a set of validated tools, assays, SOPs, and models to equip pharma to embark rapidly on proprietary small-molecule discovery programs.

BACKGROUND & SIGNIFICANCE

Clinical trial failure rates, including those for neurological disease, are extremely high.¹ The increasing number of failures due to lack of efficacy has led to the conclusion that the current preclinical pipeline is failing to correctly identify good drug targets. As a result, patients have few options and industry is disincentivized to invest in neuroscience.²

By one estimate, 50% of clinically proven drug targets are clearly linked to genetic disease, 4–5 fold greater than targets encoded by other genes in the genome that lack a link.³ Moreover, genotype/phenotype relationships can reveal causal and dose-response relationships, leading to renewed calls by industry to enable human genetics to directly inform drug discovery.⁴

Great progress has been made in elucidating the genetic architecture of PD.^{5,6} A growing number of variants and loci have emerged that exert effects across a spectrum of risk, from rare highly penetrant mutations through to common genetic variability that imparts modest risk for disease. The *SNCA* locus is a compelling example. It contains both missense and multiplication mutations associated with familial PD and risk factor variants for sporadic PD that likely increase the expression or deposition of the α -synuclein protein.⁷ Similarly, some coding mutations for *LRKK2* show incomplete but age-dependent penetrance (OR varies from 2 for G2385R to ~6-7 for ‘Mendelian’ variants such as G2019S) and also common but low-effect-size non-coding variants (OR ~1.2). Protein-coding mutations in the *GBA* gene (that cause Gaucher’s disease in homozygotes) are associated with a 5-fold increase in risk of sporadic PD in heterozygotes⁸ and predict a more aggressive disease course.⁹

Because the burden of proof is so high, identification of risk loci through large-scale GWAS analyses provides absolute surety that a risk exists and a precise estimate of the effect size.⁵ But this does not equate to a drug target. GWAS hits highlight surrogate markers (tag SNP), but the *causal* variant underlying each of these association signals and its functional consequences in vulnerable dopamine neurons or glia cells are *unknown*.¹⁰ This question is critical, as the strategy for drugging a dominant gain-of-function mutation is different than for a loss-of-function or deletion variant; indeed, pharmacologically driving the activity of a risk gene in the wrong direction may be worse than doing nothing, and could quite feasibly worsen the condition or increase the rate of disease progression. Moreover, complicating matters, many of the disease-associated GWAS variants do not encode or change protein sequence --- they are non-coding, localized up or downstream of protein-coding genes, as well as in introns or even in distant intergenic regions and gene deserts. They are as yet without a proven link to a druggable target gene. Such variants might alter enhancers or repressor elements (identifiable through characteristic histone marks¹¹ and enhancer RNA

(eRNA) expression¹²) and thereby *cis*-regulate protein-coding effector genes and effector networks. For many of the GWAS peaks linked to PD, *multiple* genes are physically localized under the peak, making it a non-trivial challenge to determine which one gene causally underlying the association signal. Thus, translating GWAS signals into a functional understanding of the disease processes and novel drug targets is a major, unresolved challenge in the post-GWAS era. Such effector genes regulated by the causal GWAS hit are likely to be critical in the disease process. The role of such genes in disease is, by definition, modulated by common variability, suggesting they are likely to have a role that is generalizable across the disease.

Collectively, the data support a model whereby familial and sporadic PD have overlapping pathophysiological mechanisms. By extension, targets identified in familial PD should have an enhanced likelihood of translational success in all PD. For example, cells from sporadic PD patients were recently found to respond to LRRK2 kinase inhibitors in a manner that would be consistent with familial mutations,¹³ supporting clinical development of drugs around this target for a broad group of patients. Moreover, the activity of β -glucocerebrosidase (the enzyme encoded by the *GBA* gene) appears impaired in brain and biofluids both of sporadic patients *and* in those carrying a *GBA* mutation.

These data also argue that there is likely to be coalescence of disease pathways across monogenic genes and risk genes.¹⁴ Genetic loci with pleomorphic risk support this notion,⁷ as do discoveries of direct interactions between proteins that were independently identified from genetics studies as causing or conferring risk of PD.¹⁵

We conclude that genetic variants proven to confer risk of PD are likely to be enriched in potentially successful drug targets for sporadic and familial PD, and that functional evaluation of these variants will produce a deeper more complete understanding of the pathophysiology of PD and help prioritize targets for a drug discovery effort.

RESEARCH DESIGN

Overview. The goal of AMP-PD Proposal 1 is to identify and substantiate putative therapeutic targets for PD by functionally evaluating these targets in iPSC-derived human neurons and astrocytes in culture, in nigral dopamine neurons and glia cells *in situ* in human brain, and *in vivo* animal model systems. The research design of Proposal 1 is made up of 3 phases:

- **Phase 0**

- **Prioritization of genetic variants.** This process will focus on the genetic characterization, analyses and prioritization of gene candidates for functional evaluation and will take into account those candidates that arise from the genetic analysis, brain platform analyses, and biomarker discovery efforts of AMP-PD. Both raw and processed data from this Phase will be shared through the AMP-PD data portal (AMP-PD Knowledge Portal) and a summary file of the genetic variables with a search function will be provided on an AMP-PD public site (e.g., the AMP-PD variant database). A Variant Prioritization Working Group of AMP-PD industry and academic investigators will work in collaboration with the Parkinson's Disease Genetics Sequencing Consortium (PDGSC) to nominate gene candidates for functional analysis.
- **Optimization and standardization of cell source(s) and differentiation protocols.** This process should take 2-3 months to complete and would coincide with the initial phase of candidate prioritization. Support for Phase 0 includes computational time and storage, FTE analytical support, related PD knowledge portal costs and costs associated with standardization of cell source(s), and differentiation protocols. Ongoing sequencing efforts are covered by other funding sources including the Department of Defense (DoD) and NIH.
- **Collection and quality-control of 100 high-quality brains of patients with PD and 100 controls.** 100 brains with PD neuropathology at various Lewy body Braak stages and 100 control brains will be selected for inclusion into the Brain Cell Platform. 140 of these have already been identified. Eligibility criteria for 100 brains with PD neuropathology will include clinical and neuropathological diagnosis of PD at various stages of Braak Lewy Body neuropathology (Braak stages 3-6 and clinical diagnosis of PD) or diagnosis of incidental Lewy bodies (Braak LB stages 1-3, subclinical) as well as high-quality tissues integrity with RIN ≥ 6 by Agilent Bioanalyzer and short PMI. PD and control brains free of a concomitant neuropathological diagnosis of other neurodegenerative diseases (e.g., no diagnosis of Alzheimer's disease according to NIA-Reagan criteria) will be selected.

- **Phase 1**

- Phase 1 will consist of two parallel platform analyses:

- **1.1. Human Functional Evaluation Platform and 1.2. Human Brain Cell Platform.** In Phase 1, the prioritized candidates nominated by the AMP-PD Variant Prioritization Working Group will move forward for functional assessment in a human cell based platform. This Functional Evaluation platform will enable analysis of variant function at both the single cell and omic levels by incorporating robotic microscopy, transcriptomics, epigenomics, and proteomics techniques. The effects of GWAS-derived common variants in PD-vulnerable dopamine neurons of the substantia nigra will be evaluated using transcriptomics, epigenomics, and targeted proteomics. Familial PD genes, low, and rare-frequency variants in the disease network will be evaluated for their role in the GWAS-variant-linked networks. To ensure that data generated by the Human Functional Evaluation, Human Brain Cell, and the Biomarkers Platform are consistent, quality control assessments and pipeline analyses will be coordinated across the three platforms (**Table 1**). Quality control standards will play a significant role in the cell based functional analysis platform. Many of these cell based quality control standards have been developed in the NIH Library of Integrated Network Cellular Signatures (LINCS) Program and will be applied to AMP-PD. Raw and processed data generated through these platforms will be submitted to the AMP-PD Knowledge Portal for integration and analyses of candidate genes and pathways for testing in Phase 2. As data integration maybe achieved through a number of different approaches, candidates nominated for *in vivo* testing will be presented to the full AMP-PD steering committee for approval. Support for Phase 1 will include costs associated with the Human Functional Evaluation Platform, the Human Brain Cell Platform, related PD knowledge portal costs, and data integration and analytical pipeline development costs.

- **Phase 2**

- Phase 2 focuses on the *in vivo* replication/validation of candidate genes and pathways identified through the Phase 1 Functional Evaluation platform. The *in vivo* model system chosen should enable comparison of brain regions and/or neuronal and glial cell types analyzed in Phase 1 and also by the Brain platform. Coordination of RNA seq, whole genome sequencing (WGS), epigenomic, and proteomic methodologies across Phase 0, 1 and 2, as well as the Brain platform and biomarker discovery efforts will enable the comparison and integration across datasets, as well as significantly increase the preclinical evidence for a target to move forward for clinical development. Support for Phase 2 will includes costs associated with the model system assessment, related PD knowledge portal costs, and data integration and analytical pipeline development costs.

Table 1: Data Types in AMP-PD for Multi-scale Integration

Biomarkers Project	Targets and Assays Project	
Study patients	Human iPSCs	Human brain cells
Whole genome analysis	Whole genome analysis	Whole genome analysis
Transcriptomics	Transcriptomics	Transcriptomics
Epigenomics	Epigenomics	Epigenomics
Proteomics	Proteomics	Proteomics
Neuroimaging	Single cell imaging	Neuropathology
Clinical data	Clinical data	Clinical data

The deliverables to pharma from Proposal 1 will be a series of potential targets directly linked to PD through genetic and/or biomarker studies and mechanistically elucidated by deep phenotyping with OMICS and imaging. The Brain platform outlined in proposal 1 will provide a critical validation step for biomarker discovery outlined in proposal 2 and pathways and targets identified in proposal 1. The functional evaluation platform outlined in proposal 1 will also

provide a set of validated tools, assays, SOPs, and models to equip pharma to embark rapidly on proprietary small-molecule discovery programs.

1.1 PRIORITIZING GENETIC VARIANTS: genetic data generation, analysis and candidate gene prioritization for evaluation in the Human Functional Evaluation and Human Brain Cell Platforms

This process will focus on the prioritization of candidate genes for analysis through the Functional Evaluation and Brain Cell platforms. Prioritization of candidates for functional analysis will be completed by the AMP-PD Variant Prioritization working group made up of both industry and academic representatives and working in collaboration with the PDGSC. Genetic data (known familial PD genes and hits from large-scale GWAS, exome sequencing, targeted sequencing, and WGS in PD; **Tables 2a** and **2b**) will be evaluated on the Brain Cell and Functional Evaluation Platforms, thereby elucidating drug targets within the mechanistic networks driven by proven genetic signals and

linked to pathophysiology and neuropathology read-outs in neurons and glia in culture and in situ in human brain. The prioritization approaches include, but are not limited to:

Genetic variants from genotyping and sequencing data. The discovery of genetic risk variants for PD is critical because these risk variants can represent factors that disrupt cellular

Table 2a. Already Available Parkinson's Disease Datasets	
Dataset	Characteristics
Mega-Meta GWAS	Genome-wide genotype data 13,000 cases, 80,000 controls.
IPDGC NeuroX	Genotyping at 260,000 variants, including 10,000 PD variants. 9,000 cases, 9,000 controls
Longitudinal NeuroX-Omni	Genome-wide and focused genotype data in patients with longitudinal data. 3500 cases (includes PPMI, PDBP, HBS)
IPDGC Whole exome	WES 2000 cases and 600 neuropathologically normal controls
PDGSC whole exome	Whole exome sequencing on 3500 cases and 6000 controls (included IPDGC whole exome above)
NABEC	WES, targeted PD gene resequencing, array-based expression, DNA methylation, sequence based expression. 400 neuropathologically normal controls
IPDGC Targeted re-sequencing	Resequencing of 17 PD loci (and known monogenic genes). 3000 cases and 3000 controls.

functions *before* clinical symptoms are present. Risk variants may be a potential source of therapeutic targets that are active *during* a phase in PD where engagement with a drug could have a significant clinical effect. To fully integrate the ongoing efforts in PD genetics, existing datasets are available from the following sources: 1) GWAS analysis (IPDGC GWAS analysis includes 20,000 cases, 100,000 controls); 2) resequencing of risk loci and loci for disease causing mutations (existing data - IPDGC (17 PD risk loci and known PD disease causing loci from approximately

Table 2b: Ongoing, New Parkinson's Disease Datasets (12-18 months)	
Dataset	Characteristics
LNG Whole genome	WGS. 4000 cases, 800 controls (includes PPMI, PDBP and HBS samples)
NINDS-funded progression genes, high-coverage, targeted resequencing	High-coverage resequencing of 24 GWAS PD loci, 13 genes related to familial PD and 5 candidate progression genes identified through preliminary analyses. 4,000 PD cases x 32,421 longitudinal assessments (includes PDBP, HBS and includes a discovery and replication phase)

3,000 cases and 3,000 controls), (future data - NIH funded study supports resequencing of 24 PD risk loci, 13 known PD disease causing loci and 5 new candidate loci linked to progression in approximately 3000 PD cases and a replication set of 960 PD cases); 3) whole exome data from 3500 PD cases and 10,000 controls; 4) emerging data on PD progression variants from the International Genetics of Parkinson Progression (IGPP) consortium of high coverage, targeted sequencing of all PD loci of 4,000 PD patients x 10 years of available longitudinal clinical data (U01-NS095736 Clemens Scherzer); 5) the Parkinson Disease Collaborative Study of Genetic Linkage (R56-NS082349 Tatiana Foroud and Jon Landers); and 6) future whole genome data from 4,000 cases and 800 controls including cases and controls from PDBP, HBS, and PPMI biomarker studies.

Specific aspects of the genetic variant prioritization process:

1. **Integration of exome, whole genome and targeted sequencing efforts.** The PDGSC has established a Google Genomics Cloud application to support the analysis of WES data, including ~3500 cases and ~6000 controls. Through Andy Singleton's direction and with the support of the DoD, the PDGSC are generating WGS on 4000 PD patients and 800 controls, including participants in the PPMI, PDBP, and HBS biomarker studies. NIH-supported targeted sequencing efforts led by Clemens Scherzer will fine map variants at 24 risk loci and 13 known PD disease causing loci. Together, this information will provide an unprecedented resource for direct risk detection and also for providing a PD-specific reference in order to facilitate PD-centric variant imputation across existing whole genome genotyped datasets (more than 20,000 cases).
2. **Integrating GWAS and QTL data from PD or control brain homogenates.** QTL data can be particularly helpful in nominating a direction of effect. All genes in credible GWAS regions will be compared against eQTL and methQTL data in both control and PD brains. Initially, this analysis will focus on data generated from a regional survey of brain expression patterns, but as the data from the Brain platform becomes available, single cell data will also be included in this analysis.

3. **Integration of data from publically available datasets.** These include: 1,309 datasets published on GEO and Array express (EMBL-EBI) PD-relevant brain regions, cell types and biofluids; CSF and serum from biomarker databases (including PPMI, and the PDBP Data Management Resource); and organism phenotypic data including from the knockout mouse project and detailed clinical data from 4,500-5,000 PD cases from PPMI, PDBP, BioFIND and HBS biomarker studies.
4. **Integration of cell-type specific data derived from the Brain Platform.** The Brain platform will utilize laser capture methodology to isolate specific neuronal and astrocyte populations in defined brain regions from PD cases and healthy control brains for analysis by RNA seq, WGS, and targeted proteomics. Data generated from analysis will be integrated with other datasets derived from Proposals 1 and 2. The Brain platform will help to further validate targets and pathways identified through the Biomarker Discovery platform, as well as potentially validating or providing new insights for functional analysis through the Functional Evaluation platform.
5. **Integration of data derived from the Biomarkers Discovery Platform outlined in Proposal 2:** Existing biomarker data and ongoing biomarker discovery outlined in Proposal 2 of AMP-PD will be integrated into the prioritization process for nominating and substantiating therapeutic targets. Some of the same data types will be generated from biomarker samples and iPSC samples (**Table 2**). A common analytic pipeline will be used to process raw omics data from both cell based assays and biomarker discovery assays that are shared across platforms. The details of the analyses are described below, but we expect that based on these analyses, some pathways and any variants associated with genes that map to those pathways may be prioritized over others.
6. **Dialog with pharma - integration of druggability and toxicity data.** An assessment of a target's druggability, availability of tool compounds or late stage clinical assets, anticipated side effect/toxicology profile, potential for development of a companion diagnostic, and feasibility of a clinical trial around a target will be important criteria to include in the target prioritization process.

1. 2. HUMAN FUNCTIONAL EVALUATION PLATFORM

The goal of this Platform of the Targets and Assays project is to carry out the functional evaluation of genetic variants to determine whether they affect disease-relevant cellular and molecular phenotypes in iPSC-derived CNS cell types. Approaches to be applied include transcriptomics, epigenomics, proteomics, WGS, and single cell robotic analysis.

iPSC lines

Table 3. PD Patient iPSC Lines	
Cause of PD	No. Lines
LRRK2 R1441C	3
LRRK2 G2019S	11
LRRK2 Y1699C	1*
LRRK2 R1441G	2*
SNCA triplication	3
SNCA duplication	2
SNCA A53T	3
Parkin ex3-4del, del255A	1
Parkin R275W	1
Pink1 R275W	1
DJ-1	2
GBA	2 + 1**
Sporadic PD	1 [†]
Sporadic PD carrying a GWAS variant	2**

*in production; [†]plus 20 from PPMI; **in production from HBS

Cell source(s) and differentiation protocols defined in Phase 0 will be utilized in the Functional Evaluation platform. Quality assurance assessments will be applied across cell types and assays. Functional evaluation will be performed in iPSC lines carrying PD disease causing mutations (LRRK2 G2019S, SNCA A53T, PINK1 P1368N, PARKIN R275W, GBA N370S and isogenic controls). iPSC lines available from the NINDS Human Cell and Data Repository, as well as other sources are summarized in **Table 3**. *SNCA* and *LRRK2* mutant lines will be used because they exhibit disease-relevant phenotypes and because of their relevance to PD. Prioritized candidate genes identified in Phase 0 will be manipulated either through CRiSPRi/a manipulation resulting in inactivation or activation of the targeted gene or through siRNA silencing or overexpression via viral delivery.

Differentiation protocols.

Existing protocols for differentiating iPSCs into DA neurons achieve efficiencies up to ~40%.^{16,17} DA neurons differentiated from iPSCs and purified using FACS exhibit a transcriptional profile that is virtually indistinguishable from human DA neurons taken from adult brain.¹⁸ That is important because a concern with differentiating other cell types from iPSCs is that the final

cell may be immature, with a profile more similar to a fetal or embryonic cell. Protocols have also been developed for differentiating iPSCs into other PD relevant cell types, including astrocytes.¹⁹ Since this is such a critical consideration for the success of AMP-PD, differentiation protocols will be evaluated during Phase 0 to optimize and standardize the cell source(s) to be used in Phase 1 for target gene manipulation and readouts.

Freezing and distribution. Based on experiences from large multi-site NIH-funded iPSC consortia, identifying a single site for production and distribution of iPSCs and differentiated cells helps to minimize variability. This can be done by scaling up differentiations, freezing down the cells at a certain stage in differentiation, and distribution of the frozen pellets to the various labs. A proven method for freezing down cells at a relatively late stage in differentiation has been established. Recovery of frozen cells is significantly improved with new equipment that precisely controls the freezing process. A centralized solution, particularly if a CRO is chosen to fulfill this duty, could also offer pharma with a ready source of cells if they want to move work internally.

Perturbations. Variants may be in coding or non-coding regions. The effects of the variant will be estimated based on the nature of the genetic variation, and WGS data from the biomarker discovery studies and the brain platform can be used to identify patients with a particular variant. If a match is found, the RNAseq data from the individual will be mined to determine if mRNA levels for that gene are altered.

To investigate how genetic variants drive pathophysiology, one approach will be to use genome editing approaches (e.g., CRISPR/Cas9) to reproduce the precise genetic variant in iPSCs. This has been used successfully to investigate PD-associated eQTL variants that affect synuclein expression.²⁰ However, variants found in the natural population may have a relatively subtle effect on protein levels or function, but potentially larger effects on gene transcription at the single cell level. The iPSC platform and available assays may be too insensitive to detect effects of the variant in the relatively short duration of most *in vitro* experiments. To complement the genome editing strategy, a more definitive perturbation of the gene associated with the variant using knockdown and overexpression approaches will be used. This strategy could make it easier to observe an effect of the gene, and also get a clearer idea about the potential that the target has for affecting PD phenotypes if it was effectively drugged. It also is faster and cheaper, so a greater number of variants could be screened.

Through the AMP-PD, tool compounds that could perturb targets pharmacologically will be identified. Although it is likely that the number of targets with associated tool compounds will be limited, if available, these compounds can directly address the druggability of a putative protein and thereby gain some insight into its tractability as a drug target—the overarching goal of AMP-PD.

Functional evaluation of cell lines

Multi-omics characterization. To understand if and how particular genetic variants effect PD risk, the actions of the genetic variants in differentiated iPSCs will be characterized with OMICs techniques, including whole genome analysis, transcriptomics, epigenomics, and proteomics. There are several reasons to use multiple techniques. Firstly, relying on a single technique provides only part of the picture and can be misleading. For example, transcriptomic gene signatures contain a mix of functionally important signals and others that are correlated, but not causal. Moreover, mRNA levels are only somewhat correlated to protein levels and protein function is modulated by multiple factors in addition to expression levels. By collecting data from a variety of orthogonal approaches, we can capture a more complete picture of the biology that a genetic variant evokes and provide unique analytical opportunities to integrate data across multiple modalities, focus on the signals that are most relevant and avoid pitfalls inherent to any single technique.

Transcriptomics. Total RNA will be isolated and quality controlled following the same procedures used for the biomarkers discovery and brain platforms and analyzed using RNA seq. A centralized resource will be used for iPSC differentiation to enable that the cell source for the omics studies is common. Raw data will be collected against a standard form structure and submitted to the PD knowledge portal. A standardized pipeline for RNA seq analysis will be established, so that all RNA seq data regardless of the platform will be processed through a shared analysis platform. The processed data set will also be available through the PD knowledge portal and summary expression data will be displayed on the PD knowledge portal public website.

Epigenomics. Epigenomics data will be derived from the same cell source as the transcriptomics data. ATAC Seq, ChIP Seq for H3K4me1, H3K27Ac, and the Illumina Methylation EPIC bead chips will be used for analysis. All data will be submitted to the PD knowledge portal.

WGS. WGS will be completed on each of the iPSC cell lines and submitted to the PD knowledge portal.

Proteomics. Targeted SRM-MS: 200 candidate proteins derived from integrative genomics analyses and known familial PD genes will be interrogated.

Use of a single cell source described above for the omic analyses follow the experimental design established by the NeuroLINCS consortium. This experimental design minimizes inherent variability in culture conditions in the various labs and addresses quality control measures to enable comparison across experiments and perturbations.

Deep phenotyping - imaging. Cell-based imaging will be a major approach to characterize the functional effects of PD-associated genetic variants in AMP-PD. Retraction of nigrostriatal projections and loss of nigral DA neurons are a pathological hallmark of PD, and these phenotypes can be recapitulated *in vitro* in PD models, including from patient iPSCs.^{16,21} Cell-based phenotypic analysis has proven to be a surprising source of novel and clinically effective therapies.

Robotic microscopy (RM) performs high-throughput (HT) longitudinal single-cell imaging analysis. RM is 100-1000 fold more sensitive than conventional high-throughput screening HTS approaches. This could be important for discovering and quantifying effects of GWA variants, which could be subtle. Because it is a single cell approach and each cell serves as its own control, it is especially well suited to collecting meaningful phenotypic data from heterogeneous cultures of iPSCs.²² Finally, the method is amenable to studying transmission from one cell to another because it tracks individual cells within networks over time. A two-tiered analysis is proposed to address:

PD cellular exam – A core set of phenotypic assays will be applied to the evaluation of all genetic variants. These have been chosen because of their perceived relevance for PD and potential for revealing common pathways by which familial and sporadic PD induces neurodegeneration and the activity of genetic variants.

1. **Disease-associated phenotypes and proteotoxic stress** – Survival and neurites will be measured in a HS unbiased fashion with RM using Kaplan-Meier analysis and dynamic measures of neurites.^{16,23-25} Synuclein and PD-associated LRRK2 mutations induce dose-dependent deficits in neurite length, survival and other cellular phenotypes even in the absence of exogenous stressors.¹⁶ In addition, exogenous synuclein or tau monomers, dimers, and fibrils can be applied to induce stress.
2. **Synuclein species, uptake and spread** – RM, coupled to super resolution microscopy, provides near EM resolution from fixed and immunostained cells. The combined approach will be used to investigate effects of variants on levels of synuclein and the production of monomers, oligomers, larger aggregates, phosphorylated species, etc. RM will also be used to detect genetic variants on the spread of neurodegeneration from one cell to its neighbors over time.
3. **Organelle trafficking and function:** Multiple cellular organelles have been implicated in PD through genetic risk variants (e.g., the lysosome by GBA mutations, mitochondria by PINK1 and Parkin, the trans-Golgi network by LRRK2, etc.). Note that these readouts, in conjunction with readouts on synuclein listed above for any given variant, could well go beyond explaining the role of the given gene in increasing risk, and also lead to a deeper understanding of the disease in general. Within the physical exam of the cell (below), biosensors exist that make it possible to visualize the structure, function, and trafficking of organelles including lysosomes, mitochondria, the Golgi apparatus, components of the secretory apparatus, etc.). Organelles are visualized with biosensors specifically targeted to them, which are used to measure trafficking in single cells by collecting short movies in a HT fashion.²⁶
4. **Cellular quality control (autophagy, lysosome, mitophagy).** Biosensors are developed for measuring a variety of quality control pathways in cell-based assays. Using photoswitchable proteins, optical pulse-labeling techniques have been invented to measure metabolism at a single cell level with RM, including the flux through the autophagy and ubiquitin proteasome pathways, as well as turnover of proteins that induce neurodegenerative disease and organelles (mitophagy).²⁷⁻²⁹ Multiplex HT assays are available to measure lysosome shape, size, number, localization, trafficking, autophagosome fusion, pH, enzymatic activity, and Ca^{2+} .
5. **Mitochondrial phenotypes** – a variety of HT cell-based assays are available, including mitochondrial mass, morphology/ fragmentation, ATP production, ROS production, etc.

Physical exam of the cell - The identity of the genetic variants and the bioinformatics analysis in Phase 0 may implicate cellular pathways and mechanisms that are not represented in the 5 components of the PD cellular exam above. Likewise, the OMICs analyses described below could offer surprising new insights into mechanisms of genetic variants that would be better investigated with additional cell-based assays. Recently, an array of over 270 biosensors designed to measure diverse cell structures and functions is being developed called the physical exam of the cell (PEC).²² Included in the list are tools to enable automated methods to optically stimulate and record electrically from

cells (Optopatch, GCaMP6F). The PEC will provide a tool box of assays to provide even deeper phenotypes around high priority targets.

Bioinformatics data integration. A variety of methods will be used to extract relevant information from data collected with individual OMICS modalities. For example, powerful computational tools, such as Enrichr and the characteristic direction method for detecting differentially expressed genes,³⁰⁻³² are superior to standard methods for analysis of RNAseq data. Data from the disparate OMICS techniques will be integrated using several techniques including network analysis.³³ Hofree et al.³⁴ pioneered a network-based approach that finds functionally relevant biological pathways. Their algorithm uses network properties to select functionally related proteins for signatures. These ideas are extended in NeuroLINCS (<http://www.neurolincs.org>) by Dr. Ernest Fraenkel^{33,35-39} to integrate data collected from patient iPSC-derived neurons and analyzed with WGA, transcriptomics, epigenomics, and proteomics into networks to identify signatures that are likely to be highly predictive and causal. The algorithms combine data from different modalities that initially appear unrelated, or even contradictory by seeking a set of physical links among the observed data and selecting a subset of the network most strongly indicated by the data. These OMICS data will be integrated with the imaging assays into a working model of variant function and perturbation experiments will be designed to test the models with additional imaging assays and OMICS assays. Supervised and unsupervised machine learning (ML) will be used to help iterate and refine pathophysiology models.²²

1.3. HUMAN BRAIN CELL PLATFORM

A key challenge in the post-GWAS era is to establish which gene functions are affected by the GWAS association signals, and secondly, to identify the causal variant. The goal of this Platform is to understand how PD-associated genetic variants regulate molecular function precisely in the cell type preferentially vulnerable to the human neurologic disease --- dopamine neurons of the substantia nigra pars compacta during various stages of subclinical and clinically manifest Lewy body neuropathology. Target gene products, circuit components, and network hubs associated with the disease variant and amenable to pharmacological intervention will be identified. The roles of familial PD genes in the driver networks will be clarified. Finally, novel exonic variants and loci linked to susceptibility or disease progression emerging from ongoing large-scale exome, targeted sequencing (TS), and WGS meta-analyses on molecular networks. Because some PD-associated variants may exert their detrimental effects preferentially through glia cells rather than dopaminergic neurons, analogous functional genomics analyses will be performed in glia cells isolated in a cell-type-specific manner from the same human brains.

One way to enrich for GWAS variants that are likely to have causal effects is to account for the genetic influence of the variant on gene expression⁴⁰⁻⁴² and protein expression.⁴³ Such effects are increasingly recognized as being of fundamental importance, as most common variants are found in non-coding regions.¹⁰ To date, the majority (~93%) of disease- and trait-associated variants emerging from GWAS lie within non-protein coding sequence. Several lines of evidence suggest the involvement of a proportion of such variants in transcriptional regulatory mechanisms, including modulation of promoter and enhancer elements⁴⁴ and enrichment within expression quantitative trait loci (eQTL).⁴⁴ To determine the *cis*-acting and *trans*-acting effects of genetic variants on the transcriptional output of the human genome precisely in vulnerable dopaminergic neurons of human brain substantia nigra (SN) (and, separately, glia cells), expression Quantitative Trait Locus (eQTL) and allele-specific gene expression analyses will be performed across the 200 dopamine neuron (and 200 glia cell) transcriptomes. Analysis of laser-captured dopamine neurons will provide higher power for detecting the most disease-relevant eQTLs than the analysis of brain homogenates that are confounded by a mixture of various neuronal and non-neuronal cell-types.^{45,46} eQTLs are genomic sequence variants (as determined by genome-wide SNP analysis) that correlate with gene-expression differences (as determined by transcriptome-wide RNA-seq analysis). eQTL studies are similar to traditional genetic-association studies, but instead of associating genetic markers with discrete traits such as disease status, eQTL studies correlate genetic markers with quantitative gene-expression levels.⁴⁷

Moreover, integrating information from chromatin state maps and other epigenomic maps will provide guidance towards the most likely causal PD-associated genetic variants regulating gene expression in specific brain cells. Chromatin immunoprecipitation, followed by high-throughput sequencing, allows to map transcription factor binding, chromatin regulators, or histone modification marks and accessible chromatin regions by DNase I hypersensitivity analysis (DNase-seq).⁴⁸

eQTL analysis has been highly successful in the study of complex diseases such as Alzheimer's, asthma, cardiovascular disease, hypertension, and obesity.^{47,49-52}

Eligibility criteria and brain banks. A growing body of literature supports the concept that individuals with brainstem α -synucleinopathy but with absent or mild symptoms probably have pre-motor or subclinical PD⁵³⁻⁶⁰ (Braak stages 1 to 3) although this is not without controversy.^{53,61} An estimated ~5-10% of individuals without recognized motor symptoms during life display typical PD neuropathology with α S-positive Lewy bodies,^{56,62} reduction of dopamine markers,^{54,55,63} and mild and select loss of ventrolateral substantia nigra neurons on autopsy.^{58,59} It is estimated that it may take more than five years from the onset and spread of pathology to the manifestation and recognition of the full clinical syndrome.⁶⁴ **Eligibility criteria for 100 brains with PD neuropathology:** (1) Clinical and neuropathological diagnosis of PD at various stages of Braak Lewy Body neuropathology (Braak stages 3-6 and clinical diagnosis of PD) or diagnosis of incidental Lewy bodies (Braak LB stages 1-3, neurologically still subclinical); (2) RIN¹³² ≥ 6 by Agilent Bioanalyzer (good RNA integrity); (3) PMI < 48 hours; (4) no pathological diagnosis of other neurodegenerative diseases (e.g., no diagnosis of Alzheimer's disease according to NIA-Reagan criteria¹³³); (5) absence of a primary intracerebral event as the cause of death; (6) absence of brain tumor (except incidental meningiomas); and (7) absence of systemic disorders likely to cause chronic brain damage. **Eligibility criteria for 100 control brains:** (1) absence of clinical or neuropathological diagnosis of PD or other neurodegenerative disease; (2) absence of neuropathological evidence of incidental Lewy bodies; criteria (3) to (7) will be the same as for cases. **Brain Banks:** Banner Sun Health Research Institute National Brain and Tissue Resource for Parkinson's Disease, Harvard Brain Tissue Resource Center, NeuroBank.

Deep molecular characterization of nigral dopamine neurons and glia cells in human brain

To systematically map genome, transcriptome, epigenome, and proteome variation in these brains and identify putative causal variants, genes, and pathways in PD-relevant dopamine neurons and glia cells the following assays will be performed:

- **Whole Genome Sequencing:** Illumina X10 (Macrogen), QC, sequence alignment, variant call – standardized pipeline corresponding to the WGS currently performed for the PDBP, HBS, and PPMI biobanks.
- **RNA Seq Cell type:** laser capture of cells, RNA extraction, linear amplification, quality control, RNA seq, read analysis (read counts), pipeline analysis (standardized format).
- **Epigenomic analysis (neuron specific):** FISH-FACS and FACS sorting of neuronal and glia cells from substantia nigra, procedures include RNA Seq and ChIP Seq for H3K4me1, H3K27Ac, and DHS-seq (TF foot printing).
- **Epigenomic analysis (region specific):** DNA methylation (Illumina MethylationEPIC bead chips).
- **Proteomics:** Targeted MRM-MS: 200 candidate proteins derived from integrative genomics analyses (see below) and known familial PD genes will be interrogated.

Bioinformatics analyses of the Brain Platform

Standard primary analyses for each pipeline and platform-specific quality control will be performed. Higher levels bioinformatics will be performed:

Identifying the effect of PD-associated genetic variants on gene and protein expression and cellular networks. The effect of lead risk SNPs identified by GWAS on *cis*-genes will be examined using gene expression Quantitative Trait Locus (eQTL) and protein expression Quantitative Trait Locus (pQTL) analyses. The *cis* effects of disease-associated risk loci identified by GWAS are central for understanding downstream molecular mechanisms of disease. However, these *cis*-genes likely also affect downstream *trans*-genes. After assigning *cis*-eQTLs for risk SNPs for PD, a causal inference test will be used to conservatively call causal correlations between the *cis*-genes and *trans*-genes by assessing the probability that an interaction is causal [SNP→*cis*-gene→*trans*-gene; false discovery rate (FDR) < 1%] and not reactive (SNP→*trans*-gene→*cis*-gene).⁶⁵ This analysis will delineate the structure of the network of genes regulated by each of the PD GWAS loci and identify key drivers for each network.⁶⁵ Moreover, comparison of the regulated networks for each loci will identify shared genes regulated by multiple PD risk loci that act as key drivers in a pan-disease *cis/trans*-gene regulatory network.⁶⁵ Beyond gene expression and protein expression, the effect of risk SNPs for PD on alternative splicing and allele-specific gene expression will be evaluated.

Identifying putative causal eSNPs using integrative genomics. GWAS loci typically span large, noncoding, intergenic regions with numerous single-nucleotide polymorphisms (SNPs) in strong linkage disequilibrium. eQTL analysis (above) enriches for variants that are likely to have causal effects. However, the abundance of eQTLs and the strong correlation structure (LD) in the genome make it likely that for some loci multiple associations between risk

SNPs and gene expression are found. Thus, eQTL analysis alone may not be able to resolve the functional variant underlying the GWAS effect. Individual-level, single-base-pair resolution functional annotations generated in this project (together with existing functional annotation databases (Conservation, ENCODE, FANTOM, Epigenome RoadMap, GTEX, etc.) will allow to pinpoint the putative causal variants accounting for the effect of gene expression and gene expression networks in a data-driven manner. H3K4me1, H3K27Ac, DHS-seq data will identify enhancers and accessible chromatin regions in neurons and glia. Methylation analysis will identify the methylation structure across gene bodies and regulatory, non-coding regions. Integration of these data with eQTLs will clarify for each locus which of the expression-linked risk variants disrupts critical genomic switches (e.g. active enhancers, alternative promoters, active transcription factor binding sites) and thereby drives gene expression and gene expression networks.

Replication with targeted gene expression assays and in independent populations. Approximately 200 candidates will be forwarded for confirmation on the gene expression level with standard analog or digital gene expression assays (e.g., qPCR or NanoString assays).

Moreover, because replication in independent populations is critical for assessing the robustness and validity of identified gene expression changes associated with putative causal GWAS variants, all statistically significant eQTLs identified in the Brain Platform will be forwarded for replication in independent data sets. Such data sets are available for eQTL replication in homogenate tissue of several hundreds of healthy control brains from GTEX, AMP-AD (control brains without AD neuropathology), and BRAINEAC. Forwarded eQTLs will be replicated in an eQTL meta-analysis across controls from these data sets (N>600). The signal is anticipated to be much lower in these homogenate brain tissue data sets due to lack of cell-type selection, type of brain region (typical frontal cortex not substantia nigra). However, because a large replication set will be used and because only a finite number of statistically significant eQTLs will be forwarded, the replication set will be powered to replicate the most robust and generalizable risk variant-gene expression associations. However, the number of false negatives is likely to be high as eQTLs exclusively found in dopamine neurons may not replicate in frontal cortex homogenates. Thus, this analysis will add information on generalizability and robustness of replicated candidates (true positives) informative for deciding which candidates to prioritize for iPSC experiments (see below). However, it does *not categorically eliminate* strong dopamine neuron-specific leads from potential consideration for mechanistic validation in iPSC-derived dopamine neurons (as some may be false negatives in the replication study).

Confirmation through targeted proteomics. Protein levels of approximately 200 candidate effector genes or from identified biochemical networks derived from these integrative genomics analyses as well as known familial PD genes will be interrogated using targeted MRM-MS in substantia nigra. Multiplexed targeted multiple reaction monitoring (MRM) or hi-res parallel reactions monitoring (PRM) mass spectrometry-based assays or Tandem Mass Tagging (TMT)⁴³ will be used. MRM and PRM assays can target hundreds of proteotypic peptides in a single sample and enable sensitive and specific quantification with high reproducibility across laboratories and instrument platforms.⁶⁶ Targeted MRM/PRM assays are typically built by incorporating proteotypic peptides from selected protein targets often determined from discovery-based data independent or data dependent peptide identification from representative cell or tissue sample groups analyzed at relatively low numbers of samples. Alternatively, assays can be refined at later stages of development when analyte numbers are relatively low using recombinant proteins for proteotypic peptide selection, retention time scheduling and transition optimization. Quantification is performed by spike-in of stable isotopically labeled peptide standards (AQUA) and can utilize single point calibration in cases requiring large numbers of targeted analytes (www.caprion.com). *Targets derived from secreted analytes may feed into Proposal 2 offering additional fluid biomarker candidates.*

Prioritizing high-value, druggable targets based on statistical significance, confirmation, replication, biology, and dialog with pharma for mechanistic evaluation on the Functional Evaluation Platform. Druggable targets will be prioritized based on the following criteria, which can be loosely grouped into data-driven, unbiased criteria (1-3) and expert-driven (pharma consultation, medicinal chemistry, availability of compounds, biology).

- Data-driven (effect size and statistical significance)
- Confirmation with secondary assays (e.g., targeted proteomics, ELISA, qPCR, etc.)
- Replication in independent samples
- Dialog with pharma partners:
 - Eliminate candidates based on toxicity
 - Evaluated druggability

- Use candidates as bait to query in-pharma chemical genetics libraries and other knowledge (toxicology, clinical data)

Application of current resources and investments. Brain Banks: NeuroBank, Harvard Brain Tissue Resource Center, Banner Sun Health Research Institute National Brain and Tissue Resource for Parkinson's Disease.

Applicable grants:

- **Grant R01 NS088538-01** 09/23/2014-09/24/2019 (Rudolf Jaenisch, PI *An iPSC based platform for functionally assessing genetic and environmental risk*; Analysis of 10 control and 10 PD brains – FACS sorted based on NeuN, also use of RNA abundance cell sorting procedure (FISH-FACS). Development of iPSC using CRISPR technology to explore enhancer regions associated with GWAS risk variants.
- **Grant U01 NS082157-01** 09/30/2012-07/31/2017 (Clemens Scherzer, PI *Biomarkers for early intervention in Parkinson's disease*; laser capture of substantia nigra pars compacta subclinical (Braak stages 1-3) and symptomatic (Braak stages 4 and 5) dopamine neurons from 50 PD brains and 50 age and gender matched healthy controls and non-coding (nc) RNA analysis by RNA seq (Illumina HiSeq2000).

1.4. Evaluation of forwarded genetic variants through in vivo models

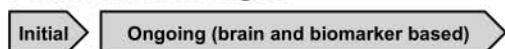
AMP-PD will use neurons and glia from patient iPSCs to mechanistically evaluate genetic variants but there are clear limitations to *in vitro* models of CNS diseases. It is difficult to recapitulate the circuitry or the precise stoichiometric and spatial relationships among different cell types in the nervous system. Thus, the selected use of *in vivo* non-human PD models, despite their limitations, can complement the functional evaluation of PD-associated genetic variants performed *in vitro*. AMP-PD has budgeted funds to investigate high priority genetic variants *in vivo* in mice. Alternatively, since most genes linked to disease are evolutionarily old (98% of genes linked to disease found in mice also are in zebrafish),³ it would be possible to evaluate a wider set of variants more inexpensively in zebrafish or invertebrate PD models.

1.5. Expected results

Integration of human genetics, human brain, human biomarkers, and human cellular mechanisms will delineate the multi-dimensional structure of the molecular networks regulated by PD variants and identify the most relevant and druggable drivers and companion biomarkers for each network. The deliverables to pharma from this project will be approximately twenty potential targets directly linked to PD through human genetic and functional studies, and mechanistically elucidated by deep phenotyping with OMICS and imaging, and a set of validated tools, assays, SOPs and models to equip pharma to embark rapidly on proprietary small-molecule discovery programs.

AMP-PD Timeline

Prioritization of targets



Project 1

Human Functional Evaluation platform

Human cell based analysis of prioritized targets

Human Brain Cell platform

Cell isolation and omic analysis

In vivo analysis of prioritized targets

Project 2

Biomarker Discovery platform

Biomarker analysis

PD AMP Knowledge Platform

Year 1

Year 2

Year 3

Year 4

Year 5

Go/No-go decision: 18 Months Milestones:

Brain Platform:

- Isolate dopamine neurons from a total of 200 brains and produce sequencing libraries
- Show pilot phase results from cell-type specific RNA sequencing and eQTL analysis of at least 100 brains to Pharma partners

iPSC Platform:

- Establish common informatics core
- Prioritize disruptive, exonic variants linked to PD susceptibility from ongoing large-scale exome, targeted sequencing (Scherzer) and whole genome sequencing projects (Singleton)
- Analyze four lines x initial set of known familial PD mutations

PROPOSAL 2: CLINICAL BIOMARKERS TO ENABLE PROOF-OF-CONCEPT (POC) TRIALS

Executive Summary. Validated biomarkers are a critical need for efficient POC trials. The PD field has made great investments in recent years to establish well-characterized clinical cohorts. Flagship public and private initiatives have put in place exceptional, clinically phenotyped, longitudinal PD cohorts --- PPMI, PDBP, Harvard Biomarkers Study, PARS, and others ---with extensive, state-of-the-art linked longitudinal biobanks. Importantly, these cohorts have been genetically characterized (Illumina exome content NeuroX SNP array) and collaborative whole genome sequencing is ongoing. Moreover, complementing this longitudinal biomarker platforms, cross-sectional biobanks have been established that address specific PD phenotypes such as BIOFIND (mid-stage PD) and the LRRK2 and GBA cohorts.

This proposal encompasses a deep molecular characterization, neuroimaging and multimodal imaging, and profiling of PD patients. The proposal would include open data and sharing to dissect new targets, dissect disease subtypes, markers tracking progression, and markers that predict progression. We would not recommend creating more infrastructure but using this opportunity for greater disease understanding *through rapid, robust, large-scale, high-throughput* biomarkers discovery. Without rigorous validation studies, discovered biomarkers lack value for therapy development and these are difficult to incentivize in the absence of a public-private partnership.

This effort epitomizes the overall goal of the AMP-PD initiative. It requires a national private-public partnership. It could not be accomplished by individual investigator-initiated grants without an overarching strategic plan. It is both financially and resource-wise beyond the scope of individual pharma companies and individual institutions. It addresses a potentially transformative objective that is critically important to bringing new drugs to patients --- yet typically out of the budget and research purview of individual pharma partners.

Most previous biomarkers studies have been limited by small sample sizes, small numbers of analytes tested, and low precision of frequently “homemade” assays. This is reminiscent of the pre-GWAS era in genetics, when myriads of small case-control association studies of candidate SNPs led to conflicting, controversial, and non-replicating findings. Now, we have an opportunity to take the biomarkers field into a new era of large, genome-scale analyses using robust platforms.

Infrastructure and Analytic Tools:

Infrastructure: The NINDS PDBP Data Management Resource (DMR) was established in 2012 to enable the standardized collection of clinical, imaging, biochemical and omics data for NINDS supported PD biomarker projects. The PDBP DMR is composed of seven modules which support the research life cycle and include: 1) ProFoRMS module, which is an electronic data entry system that uses standardized eCRFs, and also assists with participant enrollment, scheduling and protocol management; 2) the GUID module generates unique subject IDs without exposing PII and enables different types of individual level data (clinical, genomics, biosample availability, imaging) to be linked; 3) the Data Dictionary Module provides form structures, information on data elements used in standardized form structures, and links to CDISC standards where available; 4) the Data Repository Module contains information on studies in the PDBP DMR including data access and submission reports and provides tools for uploading data to the DMR, as well as downloading data from the DMR; 5) the Query Module enables a user to search across studies for shared forms, data elements, biosample availability and currently can perform a three way join of data types via the GUID; 6) the Meta Study module allows data from the PDBP data repository or other studies outside of the DMR to be downloaded and shared; and 7) the Accounts Management module provides a tool for managing a controlled access database. The ProFoRMS module is used for all perspective NINDS funded PD biomarker projects. Through this module, the PDBP DMR has quality controlled over 46,000 clinical assessments from 1500 individuals. Summary data from PDBP projects is displayed on the PDBP public website (<https://pdbp.ninds.nih.gov/data>) and is updated daily. Form structures for imaging (MR, PET, functional MR, diffusion, and CT), and genomics (WGS, exome, NeuroX, RNA seq) are developed based on NIH-wide standards for these data types. Best practice standards are applied to new data types, such that the data collected by and distributed through the DMR is compatible with other databases.

To harmonize PD biomarker studies outside of the PDBP projects, PDBP DMR support staff have worked with investigators from the MJFF/NINDS sponsored BioFIND study, the Harvard Biomarker Study, and the Arizona Sun Health National Tissue and Brain Bank for PD and Related disorders to migrate data from these studies against form current structures in the DMR. For instance, data harmonized against PDBP form structures from the BioFIND study include a biosample catalog, MDS UPDRS, MoCA, Neurological Exam, Modified Schwab and England Scale, Informed consent, Inclusion/exclusion criteria and Demographics. As the project expands the DMR can create unique form structures to capture data from these studies that is not currently represented in the DMR.